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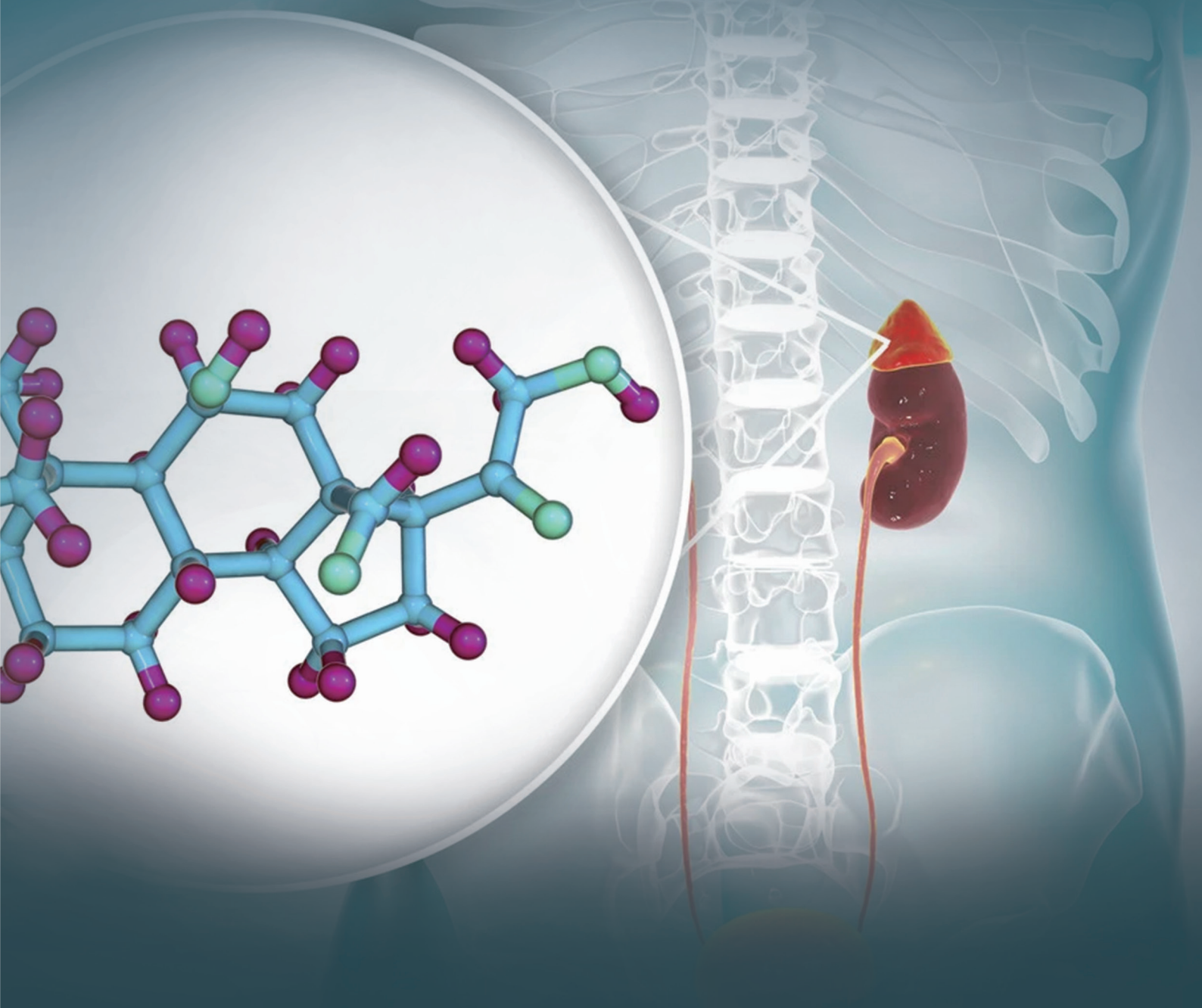

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ARTICLE

Urinary C-peptide Creatinine Ratio and Its Correlation with Parameters of Metabolic Syndrome

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ABSTRACT

To assess the correlation between urinary C peptide creatinine ratio with serum C peptide, serum insulin and its correlation with clinical and biochemical parameters of metabolic syndrome. A total of 100 subjects more than 18 years of age with metabolic syndrome according to ATP III criteria with 100 controls were included in a prospective observational study for a period of 1.5 years. Individual parameters of metabolic syndrome was higher in females with hypertriglyceridemia was most common and hyperglycaemia least common parameter of metabolic syndrome. Fasting urinary C peptide creatinine ratio and Stimulated urinary C peptide correlate significantly with fasting serum C peptide ($p<0.01$), stimulated serum C peptide ($p<0.01$), serum fasting insulin ($p<0.01$) and HOMA IR ($p<0.01$). A fasting urinary C peptide creatinine ratio of more than 1.8 nmol/mmol, stimulated urinary C peptide creatinine ratio more than 2.8 nmol/mmol and HOMA IR >2.7 can be used as a parameter to distinguish individual with and without metabolic syndrome. Urinary C peptide creatinine ratio correlate with serum C peptide and parameters of metabolic syndrome and can be used as a non-invasive simple tool to assess insulin resistance and also to distinguish patients with and without metabolic syndrome.

1. Introduction

Metabolic Syndrome (MetS) consists of physical conditions and metabolic abnormalities commonly found in association with increased risk for development of type-2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and other medical conditions [1]. Worldwide prevalence of MetS ranges from <10% to as high as 84%. Higher socio-economic status, sedentary lifestyle and high Basal Metabolic Index (BMI) were significantly associated with MetS. The prevalence of metabolic syndrome is increasing in India, both in the urban and rural areas. It has escalated in different parts of India to figures now ranging from 11% to 41% [1]. Furthermore, the prevalence is 1.5 -2 times higher in women compared to men [2,3]. The proposed central abnormality associated with MetS is insulin resistance (IR) [4]. Insulin secretory capacity can be assessed by measuring C-peptide. Serum C-peptide is commonly used as a surrogate marker of endogenous insulin secretory capacity but due to perceived practical re-

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strictions associated with sample collection its widespread use is limited. A 24 hour urine C-peptide (UCP) excretion provides an accurate means of assessing beta cell-secretory capacity and correlate with both fasting and stimulated serum insulin and C-peptide [5,6]. However, obtaining an accurate and complete 24 hour urine collection has limited the utility of this test [7-9]. Creatinine adjusted urine C-peptide concentration enables the use of 'spot' urine samples in place of 24-h urine collection. Several workers have established that high serum C peptide levels coexist with hyperinsulinemia in metabolic syndrome but there are very few studies on correlation of urinary C peptide creatinine ratio with metabolic syndrome and so we decided to explore the correlation of urinary C-peptide creatinine ratio in patients with metabolic syndrome and also its correlation with parameters of metabolic syndrome at our place.

2. Materials and Methods

A prospective observational study was conducted from January 2018 to June 2019 on subjects attending Guwahati Medical College. For calculating the sample size, at 10% population prevalence and 5.8% margin of error the required minimum sample size was 100. Total 100 Individuals more than 18 years of age fulfilling criteria for metabolic syndrome according to ATP III with 100 control subjects were included. All agreed to participate and gave oral and written consent. Criteria for metabolic syndrome according to ATP III includes any three of five criteria. Waist circumference >90 cm (M), >80 cm (F), Fasting glucose ≥100 mg/dl, Triglycerides≥150 mg/dl, HDL cholesterol<40 mg/dl (M), <50 mg/dl (F), Blood pressure->130 mm Hg systolic or>85 mm Hg diastolic. Exclusion criteria includes patients with chronic kidney disease (egfr<60 ml/min), post pancreatectomy, patients on insulin and sulphonylureas. Detailed history and thorough clinical examination were done as per proforma. Anthropometric data collected from all the patients and includes height and weight measurement. BMI calculated for all patients and recorded, waist circumference and hip circumference was recorded in all patients and waist: Hip ratio calculated. Routine investigation like Haemoglobin (Hb), Total Leucocytes Count (TLC), Differential Leucocytes Count (DLC), Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT), Kidney Function Test (KFT), Plasma glucose, HBA1C, eGFR Calculated, Thyroid function test, ECG, Chest x ray, USG abdomen. Markers of metabolic syndrome like hsCRP, serum uric acid, fasting lipid profile (Triglycerides, Total cholesterol, High Density lipoprotein, Low Density lipoprotein), fasting blood glucose (FBG) done in all cases.

Ethics approval

The Institutional Review Board of Guwahati Medical College and Hospital approved the study protocol (Number-MC/190/2007/PT-11/47).

3. Method

Patient preparation

Stimulated urine sample collected to assess maximum endogenous C-peptide response. Patients were asked to collect second void fasting urine sample after voiding early morning fasting urine. 75 gm of Glucose in water to be taken within 5-10 minute, patient should not eat anything else for the next 2 hours unless you have a hypoglycaemic episode, in which case test should be done on another day. Patient can drink water freely throughout the duration of the collection. 2 hours after collect urine and send for analysis. Sample processing done immediately for fasting C-peptide (Serum & Urine), Stimulated C peptide (120 minutes post glucose) (Serum & Urine), fasting urinary C peptide and stimulated urinary C peptide creatinine ratio calculated and finding recorded, fasting serum Insulin. HOMA IR calculated using fasting serum insulin and fasting plasma glucose and findings recorded. The C peptide and serum insulin measurement was done by electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers. Urinary creatinine was assessed by Jaffé method using Roche/Hitachi cobas c systems..

Statistical analysis

Statistical analysis was done using SPSS software. The continuous data were expressed as mean± standard deviation (SD) and range. Correlation was established by Pearson correlation method. Multilinear regression analysis was used to determine association between dependent and independent variable.

Patient and Public Involvement (PPI) statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

4. Results

Our study reveals significant gender differences with higher prevalence of metabolic syndrome in females as compared to males. Out of total 100 patients, 43 (43%) patients were male and 57 (57%) were females with higher rates of metabolic syndrome in elderly. Females have significantly

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higher baseline fasting urinary C peptide and fasting serum C peptide as compared to male (8.76±2.25 nmol/mmol; p-0.04; 1.74±0.65 nmol/mmol, p<0.0001). Similarly, fasting urinary C peptide creatinine ratio, stimulated urinary C peptide creatinine ratio (3.4±1.12 nmol/mmol, p<0.0001; 5.66±2 nmol/mmol p-0.02), serum insulin and HOMA IR (12.85±2.43 IU, p-0.04; 2.65±0.62, p-0.04) were statistically significant in female subjects as compared to males. Table 1 shows the baseline characteristics of patients and control subjects. Hypertriglyceridemia was the most common and hyperglycaemia least common component of metabolic syndrome in our study group (Table 2). There was significant positive correlation between fasting urinary C peptide creatinine ratio with Serum triglyceride (r-0.721, p<0.01), CRP(r-0.783, p<0.01), fasting serum C peptide (r-0.422, p<0.01) (Figure 1), stimulated serum C peptide (r-0.663, p<0.01) (Figure 2), Serum Insulin (r-0.528, p<0.01), HOMA IR (r-0.626,p<0.01), FBS (r-

Table 1. Baseline characteristics between cases and control

Variable	Control	Cases	P value
Age	36.69±12.9	35.95±12.1	0.672
Serum creatinine	0.82±0.1	0.83±0.1	0.578
Weight	63.69±8.83	84.82±12.33	<0.0001
EGFR	106.8±14.3	107.76±14.08	0.634
AST	19.27±4.25	40.79±9.14	<0.0001
ALT	17.32±3.87	40.94±13.84	<0.0001
Cholesterol	124.71±18.93	175.48±35.83	<0.0001
LDL	134.08±24.18	146.3±35.94	0.005
HDL	35.5±7.74	36.21±7.99	0.53
TG	207.27±44.16	208.27±47.72	0.878
Uric acid	6.01±0.85	6.02±0.87	0.902
hs-CRP	7.2±1.4	7.33±1.64	0.562
FBS	81.1±9.16	82.47±11.32	0.348
PPBS	128.96±9.02	134.78±13.16	<0.0001
Fasting urinary C peptide(nmol)	2.21±0.42	8.36±2.22	<0.0001
Stimulated urinary C peptide (nmol)	3.55±0.59	13.76±2.58	<0.0001
Urine creatinine(mmol)	2.73±0.69	2.83±0.84	0.371
Fasting serum C peptide (nmol)	0.87±0.29	1.51±0.73	<0.0001
Stimulated serum C peptide(nmol)	1.39±0.45	2.51±0.75	<0.0001
Fasting urinary C peptide creatinine ratio(nmol/mmol)	1.2±0.32	3.12±1.08	<0.0001
Stimulated urinary C peptide creatinine ratio(nmol/mmol)	2.05±0.37	5.28±1.86	<0.0001
Waist circumference(cm)	79.98±7.36	109.19±12.32	<0.0001
Hip circumference(cm)	85.62±7.71	105.88±7.57	<0.0001
W:H ratio	0.94±0.05	1.05±0.05	<0.0001
Height(cm)	161.98±9.33	162.58±9.58	0.654
Weight(kg)	65.28±9.6	84.82±12.33	<0.0001
BMI (kg/m^2)	24.63±2.34	31.97±3.31	<0.0001
HBA1C (%)	5.37±0.27	5.53±0.5	0.005
Fasting serum insulin (MIU/L)	10.98±1.46	12.43±2.32	<0.0001
HOMA IR	2.19±0.33	2.54±0.62	<0.0001

EGFR-Estimated glomerular filtration rate, AST-Aspartate transaminase, ALT-Alanine transaminase, FBS-Fasting blood sugar, PPBS-Post prandial blood sugar, TG-Triglycerides, LDL-Low density lipoprotein, HDL-High density lipoprotein, hs-CRP-High sensitivity C-reactive protein, BMI-Body mass index, HOMA IR-Homeostatic model assessment -Insulin Resistance

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0.384, p<0.01), PPBS (R-0.536 P<0.01), Waist: Hip ratio(r-0.421, p<0.01) (Table 3). Similarly there was significant negative correlation between fasting urinary C peptide creatinine ratio with HDL (r-0.195, p<0.01) (Table 4). Stimulated urinary C peptide creatinine ratio showed significantly positive correlation with Serum triglyceride (r-0.735, p<0.01), CRP (r-0.758, p<0.01), fasting serum C peptide (r-0.399, p<0.01) (Figure 3), stimulated serum C peptide (r-0.545, p<0.01) (Figure 4), Serum Insulin (r-0.580, p<0.01), HOMA IR (r-0.634, p<0.01), FBS (r-0.331, p<0.01), PPBS (r-0.386 p<0.01), Waist: Hip ratio (r-0.330, p-0.001) (Table 5&6). On multiple linear regression analysis with fasting urinary C peptide creatinine ratio as dependent variable there was significant association with stimulated serum C peptide (p-<0.0001), Serum FBS (p-0.04), Serum triglycerides (p<0.0001) and fasting serum insulin (p<0.0001) (Table 7). On multiple linear regression analysis with stimulated urinary C peptide creatinine ratio as dependent variable there was significant association with stimulated serum C peptide (p-0.03), Serum triglycerides (p<0.0001) and fasting serum insulin (p-<0.0001) (Table 8). The receiver operating characteristic (ROC) curve of fasting and stimulated urinary C peptide creatinine ratio for the diagnosis of Metabolic syndrome was depicted and the area under the curve (AUC) was calculated (Figure 5). The ROC curve identified a cut-off of fasting UCPCR ≥ 1.8 nmol/mmol and stimulated UCPCR >2.8 nmol/mmol for discriminating individual with metabolic syndrome from control population (AUC 0.980 & 0.999) with 100% sensitivity and specificity. The ROC curve identified a cut-off of HOMA IR ≥2.7 for discriminating patients with metabolic syndrome from control population (AUC 0.66) with 30% sensitivity and 95% specificity.

Table 2. Distribution of component metabolic syndrome among subjects(N-100) according to ATP III criteria

Component	Male (N-43)	Female (N-57)	Total
FBS >100mg/dl	2(25%)	6(75%)	8(100%)
TG >150mg/dl	41(43.2%)	54(56.8%)	95(100%)
	HDL		
<40mg/dl (Males)	32 (74.4%)	-	43(100.0%)
<50mg/dl (Females)	-	47 (82.5%)	57 (100.0%)
	Waist Circumference		
Males >90cm	38 (88.4%)	-	43 (100.0%)
Females >80cm	-	51 (89.5%)	57(100.0%)
Systolic blood pressure (>130mmHg)	18(43.9%)	23(56.1%)	41(100%)
Diastolic blood pressure (>85mmHg)	33(49.3%)	34(50.7%)	67(100%)

Table 3. Pearson correlation: Fasting Urinary C peptide creatinine ratio in metabolic syndrome(N-100)

Parameter	Correlation coefficient r	P Value
Fasting serum C peptide(nmol)	0.422	<0.01
Stimulated serum C peptide(nmol)	0.663	<0.01
Serum Insulin (MIU/L)	0.528	<0.01
HOMA IR	0.626	<0.01

Table 4. Pearson correlation: Fasting urinary C peptide creatinine ratio in metabolic syndrome(N-100)

Parameter	Correlation coefficient r	P Value
Low Density Lipoprotein(mg/dl)	0.078	0.44
High Density Lipoprotein(mg/dl)	-.195	<0.01
Triglyceride(mg/dl)	0.721	<0.01
Uric acid(mg)	-0.011	0.913
hs-CRP (mg)	0.783	<0.01
Fasting Blood Sugar(mg/dl)	0.384	<0.01
Post Prandial Blood Sugar(mg/dl)	0.536	<0.01
HBA1C (%)	0.099	0.105
Waist Circumference(cm)	0.114	0.261
Waist: Hip Ratio	0.421	< 0.01
BMI (kg/m^2)	0.188	0.06

Table 5. Pearson correlation: Stimulated Urinary C peptide creatinine ratio in metabolic syndrome

Parameter	Correlation coefficient r	P Value
Fasting serum C peptide(nmol)	0.399	<0.01
Stimulated serum C peptide(nmol)	0.545	<0.01
Serum Insulin (MIU/L)	0.580	<0.01
HOMA IR	0.634	<0.01

Table 6. Pearson correlation: Stimulated Urinary C peptide creatinine ratio in metabolic syndrome

Parameter	Correlation coefficient r	P Value
Low Density Lipoprotein(mg/dl)	0.049	0.628
High Density Lipoprotein(mg/dl)	-.163	0.105
Triglyceride(mg/dl)	0.735	<0.01
Uric acid(mg)	0.108	0.283
hs-CRP (mg)	0.758	<0.01
Fasting Blood Sugar(mg/dl)	0.331	<0.01
Post Prandial Blood Sugar(mg/dl)	0.386	<0.01
HBA1C (%)	0.105	0.298
Waist circumference (cm)	0.055	0.589
Waist:Hip Ratio	0.330	0.001
BMI (kg/m^2)	0.142	0.16

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Table 7. Multiple linear regression analysis with fasting urinary C peptide creatinine ratio as dependent variable

Dependent Variable: Fasting urinary C peptide creatinine ratio				95.0% Confidence Interval for B	
	B	T	Sig.	Lower Bound	Upper Bound
Fasting serum C peptide(nmol)	.091	.886	.378	-.114	.296
Stimulated serum C peptide(nmol)	.405	3.677	<0.0001	.186	.624
Triglycerides(mg/dl)	.009	4.931	<0.0001	.005	.012
Waist:Hip Ratio	2.584	1.851	.067	-.189	5.357
Fasting Blood Sugar (mg/dl)	.012	1.994	.049	.000	.024
Fasting serum Insulin (MIU/L)	.119	3.833	<0.0001	.057	.180
Low Density Lipoprotein (mg/dl)	.000	-.170	.865	-.004	.003
High Density Lipoprotein (mg/dl)	.004	.469	.640	-.013	.022

Table 8. Multiple linear regression analysis with stimulated urinary C peptide creatinine ratio as dependent variable

Dependent Variable: Stimulated urinary C peptide creatinine ratio				95.0% Confidence Interval for B	
	B	T	Sig.	Lower Bound	Upper Bound
Fasting serum C peptide(nmol)	.202	1.145	.255	-.148	.551
Stimulated serum C peptide(nmol)	.409	2.173	.032	.035	.782
Triglycerides(mg/dl)	.019	6.338	<0.0001	.013	.025
Waist:Hip Ratio	2.454	1.030	.306	-2.276	7.183
Fasting Blood Sugar (mg/dl)	.019	1.842	.069	-.001	.039
Fasting serum insulin (MIU/L)	.231	4.382	<0.0001	.126	.336
Low Density Lipoprotein (mg/dl)	.000	.074	.941	-.006	.006
High Density Lipoprotein (mg/dl)	.021	1.410	.162	-.009	.051

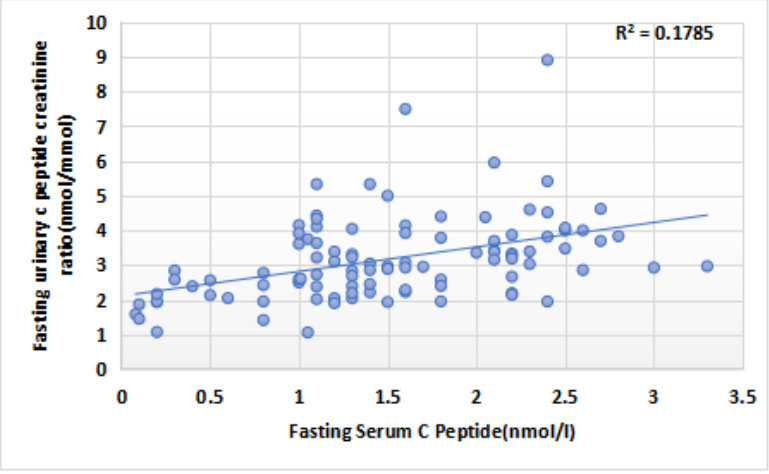

Figure 1. Scatter plot: Fasting urinary c peptide creatinine ratio and Fasting Serum C Peptide

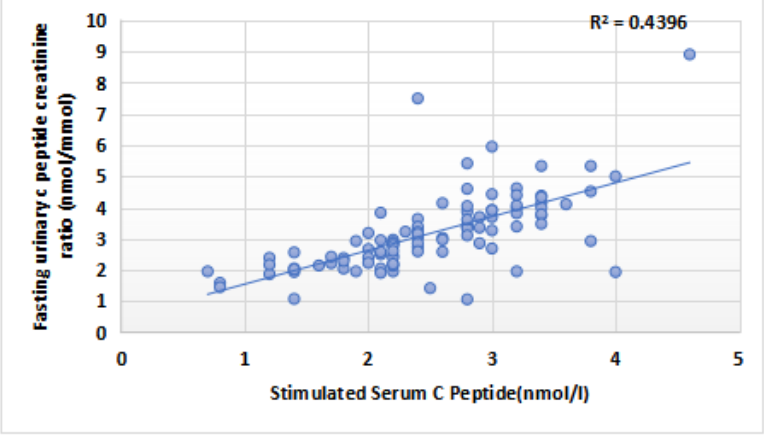

Figure 2. Scatter plot: Fasting urinary c peptide creatinine ratio and stimulated Serum C Peptide

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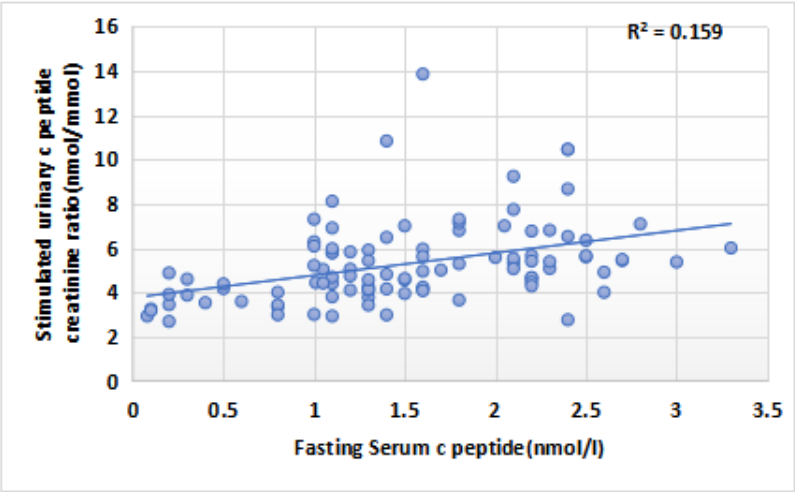

Figure 3. Scatter plot: stimulated urinary c peptide creatinine ratio and Fasting Serum C Peptide

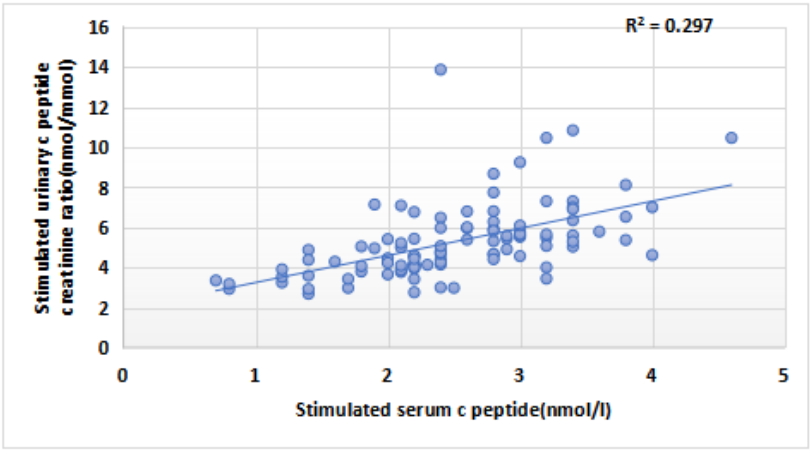

Figure 4. Scatter plot: stimulated urinary c peptide creatinine ratio and stimulated Serum C Peptide

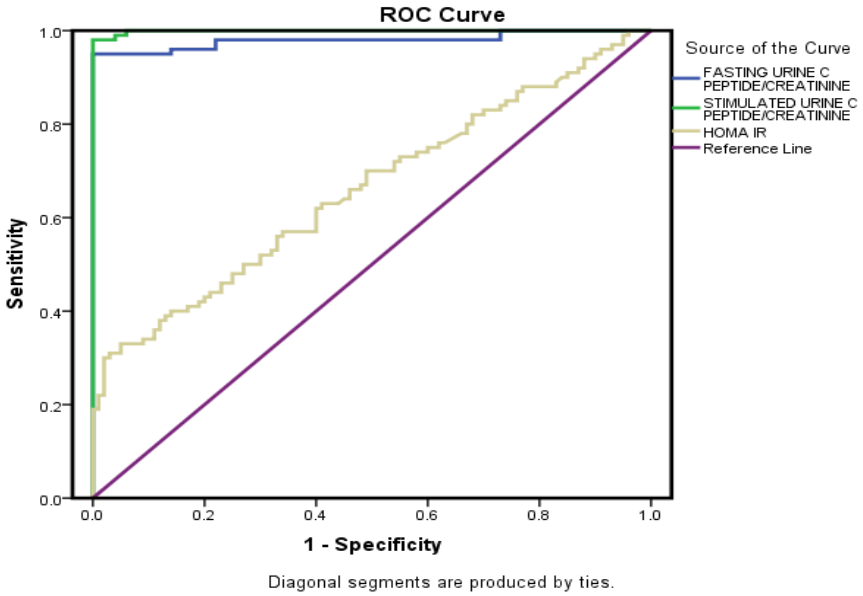

Figure 5. ROC curve to identify patients with metabolic syndrome from control population

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ROC curve to identify patients with metabolic syndrome from control population. The ROC curve identified a cut-off of fasting UCPCR ≥ 1.8 nmol/mmol and stimulated UCPCR >2.8nmol/mmol for discriminating individual with metabolic syndrome from control population (AUC 0.980 & 0.999) with 100% sensitivity and specificity. The ROC curve identified a cut-off of HOMA IR ≥2.7 for discriminating patients with metabolic syndrome from control population (AUC 0.66) with 30% sensitivity and 95% specificity.

5. Discussion

Higher levels of central obesity are found among South Asians compared to European Whites with insulin resistance is the central feature of the Metabolic syndrome. In our study, we found higher prevalence of metabolic syndrome in females (57%) as compared to males (43%), metabolic syndrome rate increases with increasing age and was higher in elderly. In a similar study Seerat Beigh [10] and D S Prasad [11] found that female have higher prevalence of metabolic syndrome as compared to males and rates are higher in older age groups. On the other hand, Anthonia o ogbera [12] found that frequency of occurrence of the metabolic syndrome was similar for men and women and it increases with age in both sexes. Hypertriglyceridemia (95%) was the most common and hyperglycaemia (8%) least common component of metabolic syndrome in our study group. Also, individual component of metabolic syndrome was higher in female subjects as compared to males. Yasmeen khan [13] in her study found hyperglycaemia as the most common parameter of metabolic syndrome followed by high Triglyceride, obesity, high blood pressure and low HDL. Seerat Beigh [10] found hypertension (38%) the most important metabolic syndrome parameters in the study subjects. Fasting urinary C peptide creatinine ratio and stimulated urinary C peptide creatinine ratio was higher in females as compared to male subjects (2.76±0.93 nmol/mmol vs 3.4±1.12 nmol/mmol, p<0.0001) & (5.66±2 nmol/mmol vs 4.79±1.56 nmol/mmol, p-0.02) which was very similar to study by Nicholas J Thomas [14] where he found that gender affects urinary C peptide excretion, with values 1.48-fold higher in women than men. This difference is because of gender differences in muscle mass in females as compared to males which leads to higher creatinine excretion (3.02±0.91 vs 2.69±0.77, p-0.05). Similarly, Kulkarni et al [15] found that urinary C peptide creatinine ratio to be 1.5 times higher in women than men. Serum fasting insulin (12.85±2.43 IU vs 11.88±2.06 IU, p-0.04) and HOMA IR (2.65±0.62 vs 2.39±0.6, p-0.04) was significantly higher in female subjects than males which is similar to study by Chen-Huan Chen [16] in Chinese population. In our study fasting urinary C peptide creatinine ratio was positively correlated with fasting serum C peptide (r-0.422, p<0.01), stimulated serum C peptide(r-0.663, p<0.01), fasting Serum Insulin (r-0.528, p<0.01), HOMA IR (r-0.626,p<0.01) and Waist: Hip ratio(r-0.421, p<0.01).Richard A Oram [17] found that in participants with normal renal function, fasting second void UCPCR correlate with serum insulin, serum C peptide, and HOMA2- IR. kulkarni et al [15] and Jose E [18] similar to our study found urinary C peptide correlated with serum C peptide and serum insulin. Mary T [19] found that the fasting urinary C peptide may serve as a practical method for estimating the secretion rate of insulin. Studies on correlation between serum C peptide with blood sugar level shows positive correlation but there are sparse studies on urinary C peptide and blood sugar level. We found fasting urinary C peptide creatinine ratio to be positively correlated with FBS (r-0.384, p<0.01) and post prandial blood sugar (r-0.536, p-0.01). HsCRP and dyslipidaemia known to be associated with metabolic syndrome and its component but studies on urinary C peptide are lacking, our study showed significant positive correlation with hsCRP (r-0.783, p<0.01) and Serum triglyceride (r-0.721, p<0.01). Yanai Wang [20] on the other hand didn't find correlation between fasting urinary C peptide creatinine ratio and triglyceride, HDL and LDL cholesterol. In our study stimulated urinary C peptide creatinine ratio has significant positive correlation with fasting serum C peptide (r-0.399 p<0.01), stimulated serum C peptide (r-545 p<0.01), fasting serum insulin (r-580 p<0.01), HOMA IR (r-634 p<0.01) which is in accordance with study conducted by Richard A Oram [17] where he showed 120 min stimulated urinary C peptide creatinine ratio correlate with serum insulin and serum C-peptide. Mary T [19] found that post prandial and 24 hour urinary C peptide excretion correlate with secretion rate of insulin. Renato pasquali [21] while evaluating clinical application of the 24-h urinary C-peptide excretion rate found positive correlation with fasting and post prandial serum C peptide. Pokhriyal BN [22] found that home urine C-peptide determination could be practical alternative to serum C-peptide in detecting severe insulin deficiency. Although no study has correlated stimulated urinary C peptide with metabolic syndrome parameters, we found significant positive correlation between stimulated urinary C peptide creatinine ratio with waist: Hip ratio (r-0.330 p<0.01), serum triglyceride (r-735 P<0.01), hsCRP (R-0.758 p<0.01), fasting blood sugar (r-331 p<0.01) and significant negative correlation with High density lipoprotein (r-241 p-0.016). We found that on multivariate analysis both fasting and stimulated urinary C peptide creatinine ratio correlate with stimulated

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serum C peptide as compared to fasting serum C peptide. Literature also suggests that stimulated serum C peptide to be more accurate as compared to fasting serum C peptide. The receiver operating characteristic (ROC) curve of fasting and stimulated urinary C peptide creatinine ratio for the diagnosis of Metabolic syndrome was depicted and the area under the curve (AUC) was calculated (Figure 5). The ROC curve identified a cut-off of fasting UCPCR ≥ 1.8 nmol/mmol and stimulated UCPCR >2.8 nmol/mmol for discriminating individual with metabolic syndrome from control population (AUC 0.980 & 0.999) with 100% sensitivity and specificity. HOMA IR cut-off of 2.5 is established for the diagnosis of metabolic syndrome with sensitivity of >70% and specificity of >60% as shown by previous studies in Indian adolescents [23]. The ROC curve identified a cut-off of HOMA IR ≥2.7 for discriminating patients with metabolic syndrome from control population (AUC 0.66) with 30% sensitivity and 95% specificity.

This study opens the door for future clinical research to establish additional criteria for diagnosis of Metabolic syndrome and to assist in refining the definition of Metabolic syndrome. In view of lack of comparative studies on urinary C peptide creatinine ratio in patients with metabolic syndrome, small sample size and observational design it is difficult to establish clinical significance of subtle abnormalities noticed in this study. Further studies are needed to verify the finding of our studies

In conclusions, urinary C-peptide is a useful indicator of beta cell function owing to sensitivity, reproducibility and convenience of the test. Urinary C peptide creatinine ratio is feasible and reliable marker of insulin secretion and insulin resistance in patient with metabolic syndrome. Fasting and stimulated urinary C peptide creatinine ratio correlate positively with markers of metabolic syndrome and can be used for differentiating individuals with and without metabolic syndrome with high sensitivity and specificity. Urinary C peptide creatinine ratio may be incorporated in diagnostic criteria in the future. Similarly, HOMA IR of >2.7 can also be used as cut off in individual at high risk of metabolic syndrome. Further work is needed to examine the potential clinical uses of this novel test and to verify the finding of our study.

6. Strength and Limitation

Very few studies have been done on fasting and stimulated urinary C peptide creatinine ratio and its correlation in metabolic syndrome.

This study opens the door for future clinical research to establish additional criteria for diagnosis of Metabolic syndrome and to assist in refining the definition of Metabolic syndrome.

In view of lack of comparative studies on urinary C peptide creatinine ratio in patients with metabolic syndrome, small sample size and observational design it is difficult to establish clinical significance of subtle abnormalities noticed in this study.

Further studies are needed to verify the finding of our studies.

Contributor Ship Statement

Dr Dipti Sarma developed the research concept presented here along with Dr Manoj Gedam and Dr Bipul Choudhury. Dr Manoj contributed to the study design and managed the database. Dr Dipti Sarma, Dr Manoj Gedam and Dr Bipul Choudhury participated in the data analysis. Dr Dipti Sarma and Dr Manoj Gedam wrote the first draft along with Dr Bipul Choudhury and were primary responsibility for final content. All authors have read and approved the final draft of the manuscript.

Conflict of Interest

No conflict of interest.

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Patient Consent

Informed verbal consent was obtained from the patient or primary caregiver.

Data Sharing Statement

Data are available upon reasonable request. Extra data is available by emailing- dr.manojvgedam@gmail.com.

References

[1] Misra A, Khurana L. Obesity and the Metabolic Syndrome in Developing Countries. J Clin Endocrinol Metab. 2008;93(11_Supplement_1):s9 -30. [PubMed].

[2] D. Prabhakaran, V. Chaturvedi, P. Shah et al., "Differences in the prevalence of metabolic syndrome in urban and rural India: a problem of urbanization," *Chronic Illness*, vol. 3, no. 1, pp. 8 -19, 2007.View at: Publisher Site.

[3] A. Misra and L. Khurana, "The metabolic syndrome in South Asians: epidemiology, determinants, and prevention," *Metabolic Syndrome and Related Disorders*, vol. 7, no. 6, pp. 497 -514, 2009.View at: Pub-

  DOI: https://doi.org/10.30564/jer.v3i2.3451

lisher Site | Google Scholar.

[4] John B. Buse, Kenneth S. Polonsky, Charles F. Burant. Type 2 Diabetes Mellitus. In: Williams textbook of endocrinology. Shlomo Melmed, Kenneth S. Polonsky, P. Reed Larsen, Henry M. Kronenberg (ed), Elsevier Saunders.12th edi., 2011.chap.31.pp 1371-435.

[5] Gjessing HJ, Matzen LE, Froland A, Faber OK. Correlations between fasting plasma C-peptide, glucagon-stimulated plasma C-peptide, and urinary C-peptide in insulin-treated diabetics. Diabetes Care 1987;10:487-90.

[6] Huttunen NP, Knip M, Kaar ML, Puukka R, Akerblom HK. Clinical significance of urinary C-peptide excretion in children with insulin- dependent diabetes mellitus. Acta paediatrica Scandinavica 1989;78:271-7.

[7] Meistas MT, Zadik Z, Margolis S, Kowarski AA. Correlation of urinary excretion of C-peptide with the integrated concentration and secretion rate of insulin. Diabetes 1981;30:639-43.

[8] Aoki Y. Variation of endogenous insulin secretion in association with treatment status: assessment by serum C-peptide and modified urinary C-peptide. Diabetes Res Clin Pract 1991;14:165-73.

[9] Cote AM, Firoz T, Mattman A, Lam EM, von Dadelszen P, Magee LA. The 24-hour urine collection: gold standard or historical practice? American journal of obstetrics and gynecology 2008;199:625 e1-6.

[10] Beigh SH, Jain S. Prevalence of metabolic syndrome and gender differences. *Bioinformation*. 2012;8(13):613 -616.
DOI: 10.6026/97320630008613.

[11] Prasad DS, Kabir Z, Dash AK, Das BC. Prevalence and risk factors for metabolic syndrome in Asian Indians: A community study from urban Eastern India. *J Cardiovasc Dis Res*. 2012;3(3):204 -211.
DOI: 10.4103/0975-3583.98895.

[12] Ogbera, A.O. Prevalence and gender distribution of the metabolic syndrome. *Diabetol Metab Syndr* 2, 1 (2010).
DOI: 10.1186/1758-5996-2-1.

[13] Prevalence of metabolic syndrome crossing 40% in Northern India: Time to act fast before it runs out of proportions Khan Yasmee, Lalchandani Arati, Gupta Ajesh Chandra, Khadanga Sagar, Kumar Sanjeev.

[14] Thomas, N. J., Shields, B. M., Besser, R. E. J., Jones, A. G., Rawlingson, A., Goodchild, E., … Hattersley, A. T. (2012). The impact of gender on urine C-peptide creatinine ratio interpretation. *Annals of Clinical Biochemistry*, *49*(4), 363 -368. https://doi.org/10.1258/acb.2011.011164.

[15] Urinary c-peptide and urine c-peptide/creatinine ratio (ucpcr) are possible predictors of endogenous insulin secretion in t2dm subjects - a randomized study kulkarni c m1, sumangala patil2.

[16] Correlation of fasting serum C-peptide and insulin with markers of metabolic syndrome-X in a homogeneous Chinese population with normal glucose tolerance a,c, c b * Chen-Huan Chen, Shih-Tzer Tsai, Pesus Chou aDepartment of Social Medicine, National Yang-Ming University, Taipei, Taiwan bCommunity Medicine Research Center, National Yang-Ming University, Taipei, Taiwan cDepartment of Medicine, Veterans General Hospital-Taipei, Taipei, Taiwan.

[17] Oram RA, Rawlingson A, Shields BM, et al. Urine C-peptide creatinine ratio can be used to assess insulin resistance and insulin production in people without diabetes: an observational study. BMJ Open 2013;3: e003193.
DOI: 10.1136/ bmjopen-2013-003193.

[18] Urinary C-Peptide Excretion: A Novel Alternate Measure of Insulin Sensitivity in Physiological Conditions Jose E. Galgani1, Lilian de Jonge1, Jennifer C. Rood1, Steven R. Smith1, Andrew A. Young2 and Eric Ravussin1 Obesity (2010) 18, 1852 -1857.
DOI: 10.1038/oby.2010.70.

[19] Correlation of Urinary Excretion of C-Peptide with the Integrated Concentration and Secretion Rate of Insulin MaryT Meistas, Zvi Zadik,Simeon Margolis, A Avinoam KowarskiDiabetes Aug 1981, 30 (8) 639-643.
DOI: 10.2337/diab.30.8.639.

[20] Wang Y, Gao Y, Cai X, et al. Clinical Implications of Urinary C-Peptide Creatinine Ratio in Patients with Different Types of Diabetes. *J Diabetes Res*. 2019;2019:1747684. Published 2019 Aug 7.
DOI: 10.1155/2019/1747684.

[21] Pasquali, R., Biso, P., Baraldi, G. et al. Acta diabet. lat (1983) 20: 153. https://doi.org/10.1007/BF02624916.

[22] URINE C-PEPTIDE TEST: A NOVEL NON-INVASIVE TECHNIQUE FOR DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH TYPE-1 DIABETES Pokhriyal BN*, Thorat K, Dubey R, Limaye DA, Joshi YM and Kadam VJ IJRPC 2012, 2(2).

[23] https://www.researchgate.net/publication/259499343A study of Insulin Resistance by HOMA-IR and its Cut off Value to Identify Metabolic Syndrome in Urban Indian Adolescents.

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ARTICLE

The Association of Non Viral Liver Diseases from NAFLD to NASH to HCC with the Pandemic of Obesity, Type 2 Diabetes, or Diabesity & Metabolic Syndrome Etiopathogenetic Correlation along with Utilization for Diagnostic & Therapeutic Purposes-A Systematic Review

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ABSTRACT

Earlier we have been reviewing the etiopathogenesis (EP) of obesity, type2 Diabetes mellitus (T2DM), Metabolic Syndrome (MetS), Non Alcoholic Fatty Acid Liver Disease (NAFLD) non alcoholic steatohepapititis (NASH), along with its propagation to Hepatocellular carcinoma (HCC) in addition to their therapies exhaustively. T2DM continues to be a major health issue with reaching epidemic to pandemic proportions. Liver disease includes a spectrum of liver injury varying from isolated steatosis known as Non Alcoholic Fatty Acid Liver Disease (NAFLD) to HCC. Clinically it has been observed that the coexistence of NAFLD as well as T2DM is prevalent. T2DM aids in the biological events that results in escalation of robustness of NAFLD that constitutes the primary etiology of chronic liver diseases. In the past 2 decades the incidence of nonviral NAFLD/NASH, obtained HCC has been escalating at a fast pace. In view of no appropriate agents for therapy of NAFLD/NASH, a thiazolidenedione group of drug pioglitazone used for T2DM therapy is utilized occasionally. Thus here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review libraryutilizingtheMeSHterms like T2DM; MetS; NAFLD; NASH; HCC; WAT; BAT; VisceralAT; Obesity; BMI; Adipocytokines; adiponectin; leptin; resistin; visfatin; irisin; Hepatokines; angiopoietin like protein 2; hepatosscin; retinol binding protein 4; treatment like pioglitazone; liraglutide; elafibranor CVC (cerviciroc); obeticholic acid; aramchol; selonosertib; simtuzumab; Oxidative stress(OS); insulin resistance (IR) from 1980's to 2021 till date. We found a total of 1050 articles out of which we selected 236 articles for this review. No meta-analysis was done. Hence diagnosis avoidance in addition to treatment of the generation as well as propagation of NAFLD/NASH are significant areas needing tackling. Thus here we have summarized the EP of NAFLD/NASH, as well as NAFLD/NASH, obtained HCC along with the present advantageous therapies under trial, for NAFLD/NASH. Moreover how adipocyte obtained adipokines along with liver obtained hepatokines might work as both diagnostic in addition to therapeutic targets from NAFLD to HCC.

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1. Introduction

Earlier we have been reviewing the etiopathogenesis (EP) of obesity, type2 Diabetes mellitus (T2DM), Metabolic Syndrome (MetS), Non Alcoholic Fatty Acid Liver Disease (NAFLD) non alcoholic steatohepapititis (NASH), along with its propagation to Hepatocellular carcinoma (HCC) in addition to their therapies exhaustively [1-24] [besides many more]. T2DM, altogether with obesity, NAFLD represents the commonest liver disease, associated -in about 30% of the general population [25]. The properties of NAFLD are hepatic triglycerides (TG), collection in addition to insulin resistance (IR) [26]. This is basically the hepatic presentation of Metabolic Syndrome (MetS) along with spans a problem encompassing benign with hepatic steatosis to NASH [27]. Widely the 2 are clubbed as Non Alcoholic Fatty Acid Liver (NAFL) as well as NASH [28]. NAFL represents isolated steatosis, whereas NASH possesses properties of steatosis, lobular inflammation (alias infiltration by inflammatory cells), hepatocellular ballooning in the existence or absence of fibrosis [29]. NASH is the one having maximum aggressiveness of the NAFLD, possesses capacity of propagation to continuous fibrosis, with a direct correlation with the risk of Hepatocellular carcinoma (HCC) generation that might be a major reason for morbidity as well as mortality stimulated by liver failure (Figure 1) [25,30]. Prevalence of NASH is about 30% in case of patients with NAFLD [31]. Roughly 20% of patients with NASH having fibrosis propagate to cirrhosis [32]. Liver cirrhosis exists in just 50% of NAFLD-associated HCC [33]. Incidence of NAFLD-associated HCC without cirrhosis is about 8% of total HCC patients [34], while total incidence rate of HCC in NAFLD as well as NASH varies from 2-13% [35].

In the clinical scenario NAFLD is present along with T2DM, obesity, influencing synergism action resulting in greater robust liver failures [36]. Prevalence of NAFLD is thought to be about 75% in cases with T2DM along with 90% in obese cases, that point to a significant association of NAFLD with T2DM along with obesity [37]. NAFLD participates significantly in escalated incidence of T2DM in addition to its complications [28]. Further T2DM exacerbates NAFLD as well to a more robust type of NASH, fibrosis as well as HCC (Figure 1) [37,38].

HCC, represents a highly aggressive cancers [39]. Earlier hepatitis C virus was believed to the commonest etiology of HCC [40], although recently it has been illustrated that till 50% of new onset HCC cases did not have a viral etiology [41]. The causation of NAFLD/NASH stimulated HCC is highly complicated, which is correlated with a lot of modes like cellular plasticity, inflammation, apoptosis, cell cycle as well as cell demise [42]. Hence therapy of HCC is tough. Moreover it is essential that concentration is done for avoidance of NAFLD/NASH propagation by treating them earlier as well as avoidance of its propagation towards irreversible chronic liver Diseases like cir-

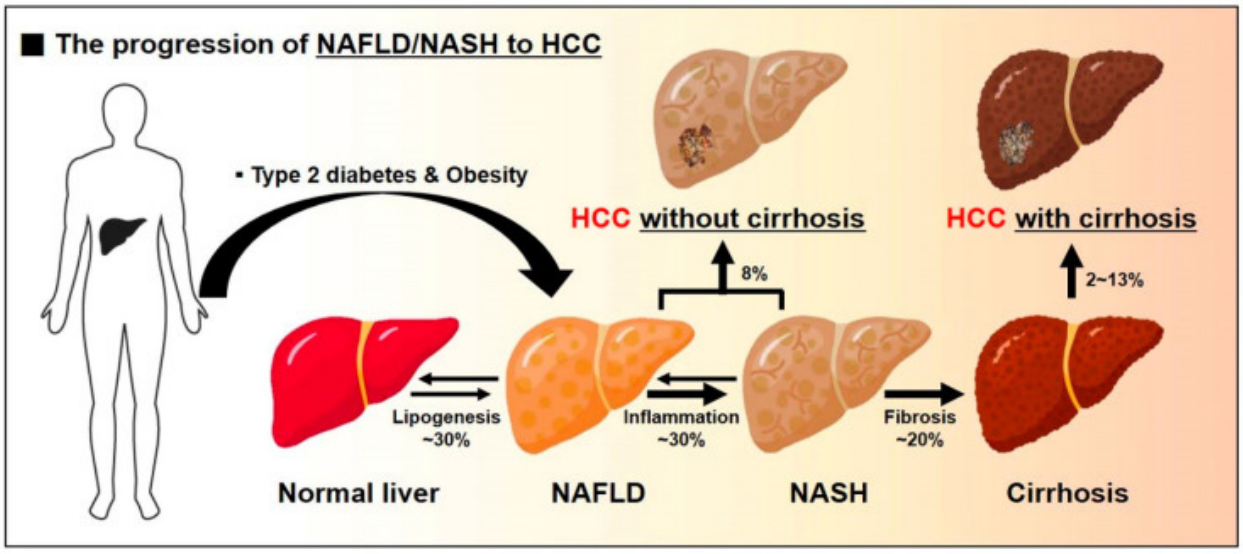

Figure 1. The progression of NAFLD/NASH to HCC

Legend for Figure 1

Courtesy ref no-30-Type 2 diabetes and obesity aggravate the progression of NAFLD/NASH to HCC. Clinically, type 2 diabetes coexists with NAFLD, and it aggravates NAFLD to more severe forms of NASH, hepatocirrhosis, and HCC, leading to a metabolically worse phenotype.

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rhosis as well as HCC. No FDA approved drugs exist till date.

Besides have reviewed a lot of therapies for NAFLD, trials under way for NAFLD/NASH therapy, we had reviewed the role of adipocytokines in obesity as well as T2DM associated heart failure (HF). Here we have tried to update on EP of NAFLD/NASH, as well as NAFLD/NASH associated HCC, besides the present beneficial therapies for NAFLD/NASH under trials. Moreover the initiation of as well as propagation can get influenced by adipokines/organokines liberated from Metabolic organs when Metabolic impairment exists like T2DM as well as obesity [43]. Thus here we have concentrated on organokines liberated by AT as well as liver. That are key organs for controlling of lipid metabolism. Newer understanding with regards to adipoklines/hepatokines which might serve as potential diagnostic as well as therapeutic targets in NAFLD/NASH as well as NAFLD/NASH obtained HCC. These are believed to be biological markers which can anticipate robustness of NAFLD from NAFLD to HCC.

Thus here we carried out a systematic review on the association of various metabolic disturbances in the initiation of various liver disorders ranging from NAFLD to NASH and further towards HCC.

2. Methods

Thus here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like T2DM; MetS; NAFLD; NASH; HCC; WAT; BAT; VisceralAT; Obesity; BMI; Adipocytokines; adiponectin; leptin; resistin; visfatin; omentin; irisin; Hepatokines; angiopoietin like protein 2; hepatosscin; retinol binding protein 4; treatment like pioglitazone; liraglutide; elafibranor CVC (cerviciroc); obeticholic acid; aramchol; selonosertib; simtuzumab; Oxidative stress(OS); insulin resistance (IR) from 1980's to 2021 till date.

3. Results

We found a total of 1050 articles out of which we selected 236 articles for this review. No meta-analysis was done.

4. Discussion

4.1 Etiopathogenesis (EP) of Non Alcoholic Fatty Acid Liver Disease (NAFLD) as well as Non Alcoholic Steatohepapititis (NASH)

Disturbed Balance -among fatty acids(FA) Metabolism

NAFLD represents the commonest cause of chronic liver disease. NAFLD occurs, secondary to escalated triglycerides (TG), collection in the liver [26]. Hence the balance among FA input as well as -output is key [44]. Implying that generation of NAFLD takes place if levels of exogenous FA uptake (by dietary ingestion along with adipose tissue (AT) lipolysis) as well as endogenous FA generation (DNL in liver is greater than the liberation of FA (FA oxidation, lipolysis, as well as FA liberation in very low density lipoprotein (VLDL) TG) from liver (Figure 2).

The liberation of FA from AT as well as effectiveness of FA uptake by liver are escalated by about 59% in cases of NAFLD [45], Liver FA is based on the number as well as action of specific FA transporter as well as FA carrier proteins like FA translocase (FAT, CD36), FA transport polypeptide [FAT]) as well as, fatty acids binding protein (FABP) [46]. Like hepatic expression of FAT/CD36 is significantly escalated in cases with NAFLD, as well as hepatic expression of FABP4 as well as FABP5 is intricately correlated with intrahepatic TG collection.

In about 26% of patients, the method of aiding liver FA pool is hepatic Denovo lipogenesis (DNL) [47]. DNL represents metabolic event which is implicated in generation of new FA from escalated glucose [48]. It significantly aids in hepatic lipid collection in etiopathogenesis of NAFLD [48]. The activation of 2 Transcription factors (of sterol regulatory element binding protein 1c (SREBP1c), as well as carbohydrate responsive element binding protein [ChREBP]), enhanced by insulin as well as glucose reaction to dietary carbohydrate [49]. They possess synergistic significant part in coordinated control of hepatic DNL. In rest 15% of patients of NAFLD, FA pool is obtained from diet TG. That is correlated with chylomicron [45].

The maximum lucrative theory in etiopathogenesis of NAFLDis "2hit" posit [50]. 1st hit is IR, secondary to escalated FA flux, 2^{ND} is inflammation, correlated with gut obtained endotoxins, Oxidative stress (OS) as well as mitochondrial impair. It is intricately associated with NAFLD-NASH.

Endotoxin behavior

NAFLD as well as other insulin resistance (IR) disease are correlated with activation of innate immune system=>chronic inflammation [51]. Recently gut obtained endotoxin, like lipopolysaccharides (LPS) have been posited to possess a key part in liver inflammation secondary as well as propagation to chronic Liver Disease [52]. Normally, Endotoxin can get absorbed from the lumen of the intestine into theportal venous system in addition to absorbed endotoxin would get cleared fast by the reticulo endothelial system, specifically kupffer cells [53]. Never-

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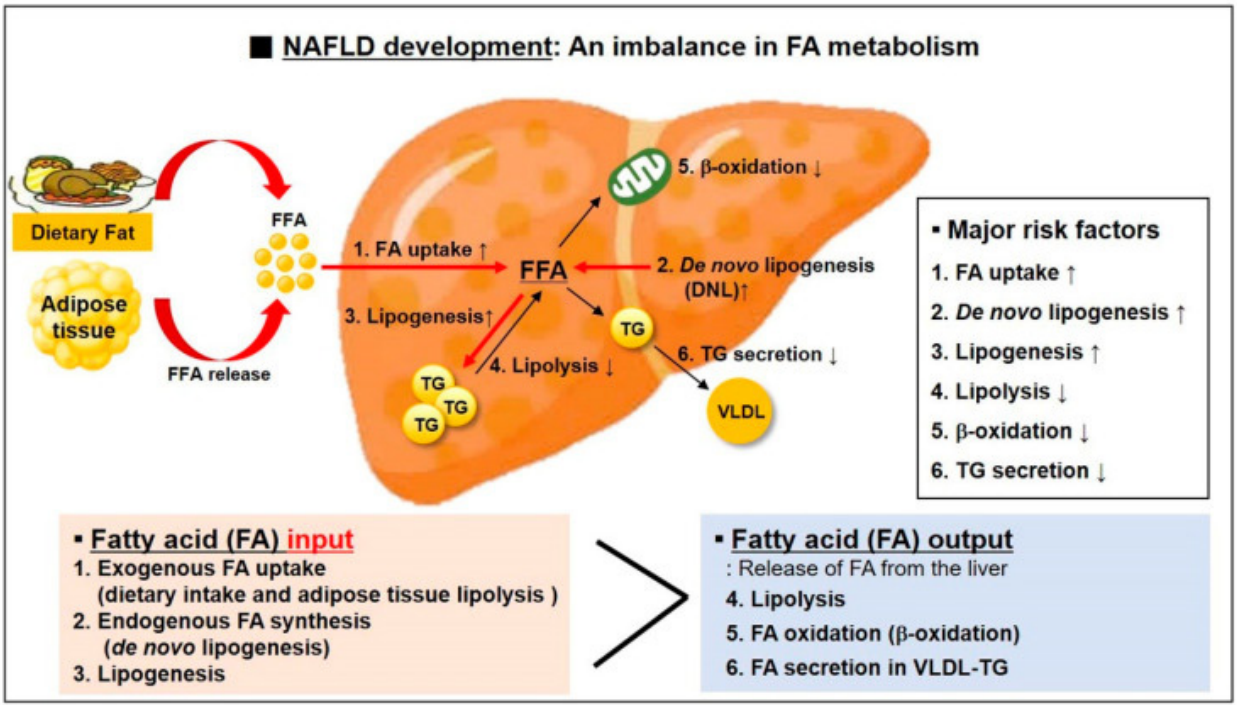

Figure 2. NAFLD development: An imbalance in FA metabolism

Legend for Figure 2

Courtesy ref no-30-NAFLD development is caused by an imbalance in the intrahepatocellular fatty acid (FA) metabolism. Hepatic TG accumulation is promoted when the FA input is greater than the FA output in the liver. The greater part of FA taken up by liver is mainly derived from the lipolysis of subcutaneous adipose tissue TG. Another major source of FA in the liver is derived from de novo lipogenesis that converts excess glucose into FAs. On the other hand, the consumption of FA is possible through the signaling pathway involved in lipolysis, β-oxidation, and TG secretion (→: signaling pathways related with TG accumulation by FA, →: signaling pathways related with the consumption of FA).

theless, obesity, type2 Diabetes mellitus (DM) along with other nutritional parameters can change intestinal permeability as far as bacterial excessive growth leading to amucosal barrier that becomes leaky resulting in bacterial transportation, that points to the liberation of endotoxin into the systemic circulation [54]. These invasive pathogenic deleterious by products have an impact on the liver lipid collection along with acceleration of proinflammatory in addition to fibrosis events [53].

The part of LPS from gut microbiota (GM) in the generation of NAFLD as well as NASH has been highlighted [54]. Circulating LPS amounts small intestinal permeability, along with bacterial excessive growth are escalated in cases of NAFLD, with these factors being correlated with the robustness of hepatic steatosis [54,56]. Livers getting blood directly from the portal vein remain the major targets of LPS, alias endotoxin, with LPS toll like receptor 4 (TLR4) being one of the key pathways for the generation of NAFLD. In case of mouse models, LPS infusion causes stimulation of hepatic steatosis in addition to hepatic insulin resistance, along with hepatic weight escalation [57]. LPS results in acceleration of liver damage in mice receiving a diet lacking methionine-choline [58]. The LPS binding protein LBP-CD14 complex results in stimulation of TLR4, that is necessary cascade needed for inflammatory propagation [59]. Once LBP deletion occurs it ameliorates inflammation modulated liver damage [60]. TLR4 possesses the characteristics of stimulation of nuclear factor κB (NFκB) in addition to liberation of proinflammatory cytokines like interleukin-1β (IL-1β), Tumor necrosis factor alpha (TNFα) as well as IL-6 [61]. Further it has the ability of recalling damage associated molecular patterns (DAMP), which get liberated from damaged cells, as well as modulates FA-stimulated inflammation [51,62]. In the form of -Pharmacological treatmentsin NAFLD as well as NASH which target the microbiome, IMM-24 (an anti-LPS antibody), solithromycin (next generation macrolide antibiotic) along with TLR4 antagonist [63].

Oxidative stress

Chronic Oxidative stress (OS) is crucial modes resulting in liver damage in NAFLD. Oxidative stress is a

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process occurring generally in NAFLD as well as NASH secondary to escalated generation of Reactive oxygen species (ROS) [64]. ROS in addition to lipid per oxidation can reason out maximum histological parameters of NAFLD as well as NASH [65]. In case of hepatic steatosis patients, mitochondrial ROS Oxidizes hepatic fat deposits along with ROS stimulated Fas ligand expression can generate apoptosis [65]. Both peroxidation of along with intra cellular membrane can directly result in apoptosis stimulation as well as necrosis [65]. The robustness of lipid peroxidation is associated with the robustness of steatosis in addition to can reason out the correlation among the robustness of steatosis in addition to the chances of necrosis inflammation along with fibrosis in NASH [66]. ROS that is a critical factor in the etiopathogenesis of NASH, can result in a self created cycle of lipid peroxidation as well as further cause ROS generation [67]. Alteration of -mitochondrial DNA can result secondary to products generated by lipid peroxidation as well as result in stimulation of the transcription factor nuclear factor κB (NFκB), which causes upregulation of TNFα [68]. Hence it further aids in dysfunctional mitochondrial respiration in addition to escalation of ROS generation [68].

Escalation of mitochondrial β-oxidation of FFA is a significant generator of ROS in NAFLD as well as NASH [69]. Enhancement of FFA flux during early NAFLD stage cause activation of mitochondrial FA-oxidation (FAO), which points to an early liver compensation modes for hampering liver fat collection along with sustenance of liver lipid homeostasis [26]. In case of NAFLD as well as NASH mitochondrial FAO is further escalated or minimum conserves in the form of a compensation reaction. The disturbed balance among mitochondrial FAO as well as electron transport chain (ETC) would aid in escalation of ROS generation by escalated leaking of electrons from the ETC [26,69]. ROS stimulated lipid per oxidation results in inflammation along with hepatic fibrogenesis via the stimulation of hepatic stellate cells (HSC's) [70].

Trusted circulation markers which might point OS in cases with NAFLD have got documented. Urinary 8-iso prostaglandin F2α (8-isoPGF2α) is believed to be trusted pointer of OS in vivo [71], as well as soluble NOX2-obtained peptide (s-NOX2-dp) are further agreed upon as marker that is correlated with ROS production on stimulation of NOX2, that is a member of NADPH-oxidase family [72]. Enhancement of urinary amounts of 8-isoP-GF2α as well as serum soluble NOX2-obtained peptide are believed to be [73] trusted pointers of oxidative stress in case of chronic inflammation along with metabolic disease [73]. Further the utilization of these markers can be done for OS regarding anticipation of robustness of liver injury in NAFLD [74]. LPS is a significant constituent of outer membrane of gram negative bacteria which results in stimulation of exacerbation of inflammation as well as Oxidative stress [75]. Enhancement of circulating amounts of NOX2 as well as LPS in NAFLD point to a potential part in gut obtained LPS in systemic NOX2 stimulation [76]. Moreover -s- NOX2-dp -amounts -possess a positive correlation of histological grading with steatosis, inflammation, ballooning, fibrosis as well as NAFLD activity score (NAS) [76]. Gut obtained LPS might result in activation of TLR4, as well as TLR4 – modulated NOXs activation can lead to generation of ROS by macrophage infiltration [77]. This can aid to hepatic steatosis in addition to IR [77].

Nevertheless, the variablility of metabolic alterations take place in NAFLD are not enough to get reasoned out by "2 hit" posit. Maximum metabolic conditions like obesity, T2DM, Metabolic Syndrome (MetS), dyslipidemia work as the risk factors for generation of NAFLD by the "multiple hits" implicating a lot of factors (Figure 3) [78]. These "multiple hits" are bioactive molecules liberated from AT, nutritional factors as well as environmental factors [78].

4.2 Attractive Treatment in NAFLD as well as NASH

With the recently advocated that pioglitazone, along with high dosages of Vitamin E, efficaciously result in amelioration of escalation of histological alterations in cases of NASH [79]. Conversely metformin has no such action in NAFLD patients [80], as well as ursodeoxycholic acid (UDCA), has no influence on liver histological alterations, inflammation, or fibrosis in patients with NASH [82]. Following are certain Pharmacological examples under Clinical trials as well as might work out as promising agent for NASH treatment (Figure 4). In addition, the metabolic profile along with liver histology correlated effectiveness of these attractive drugs [19,20,81].

Pioglitazone

Pioglitazone represents an anti diabetic drug thiazolidenediones (TZD) class utilized for T2D treatment [83]. TZD'S are further referred to as glitazones. Two TZD's are presently approved by FDA for montherapy or combination treatment with metformin as well as sulfonylureas for T2D treatment [84]. TZD's meant for insulin sensitization aid in controlling glycemia along with insulin resistance (IR) [84]. The maximum significant benefit of TZD's was that hypoglycemia doesn't result secondary to its utilization with single treatment, with it not being contraindicated in patients presenting with renal disease [85].

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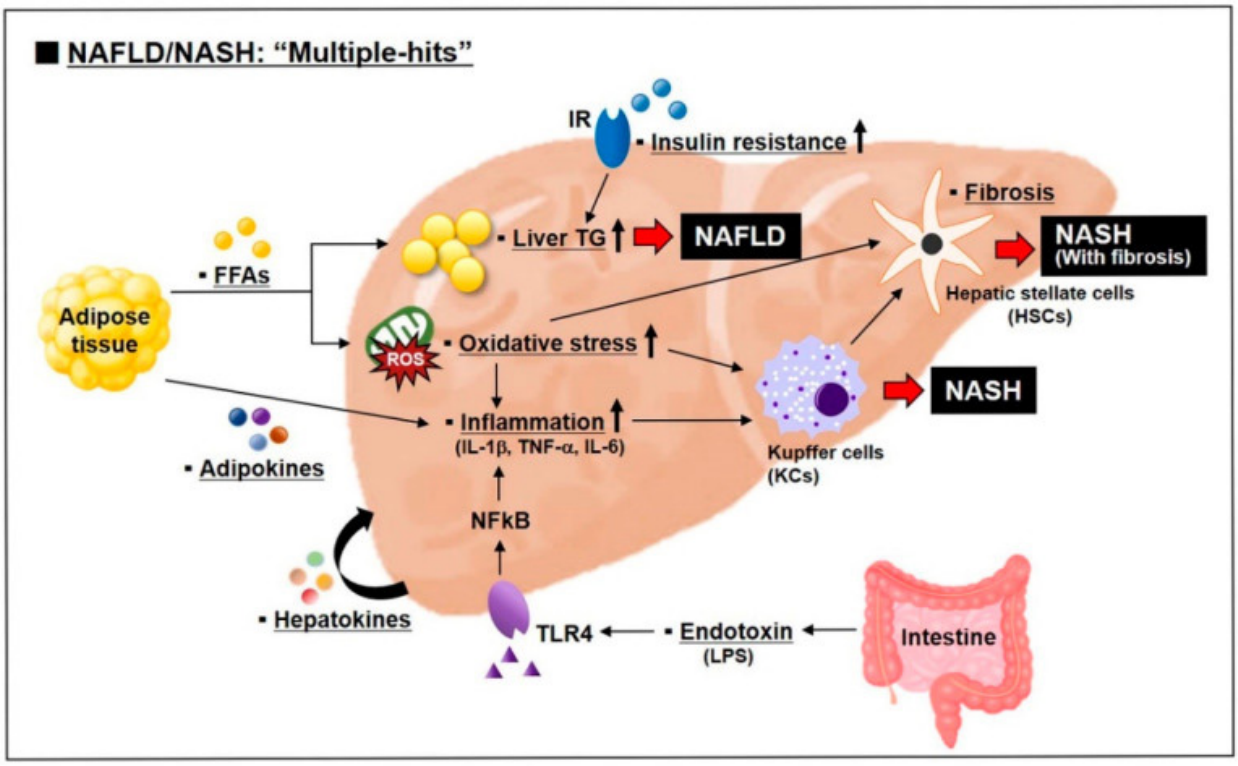

Figure 3. NAFLD/NASH: "Multiple-hits"

Legend for Figure 3

Courtesy ref no-30-Multiple-hits pathogenesis of NAFLD and NASH. NAFLD begins with hepatic lipid accumulation and insulin resistance, and progresses to NASH with the concert of various factors such as inflammation, endotoxin, organokines (adipokines and hepatokines), and oxidative stress. (▪: Factors related with multiple-hits).

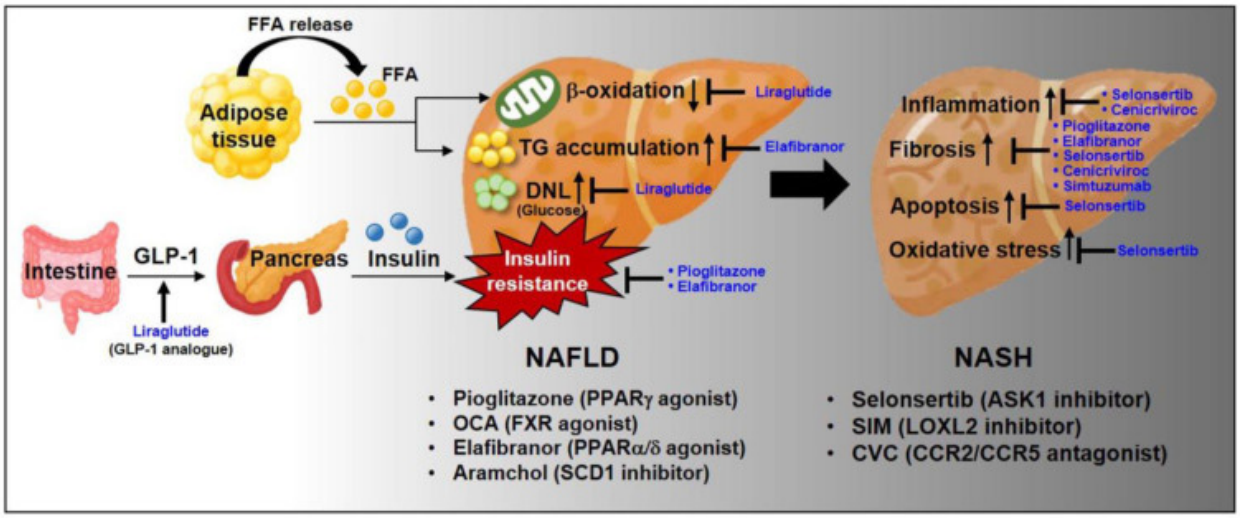

Figure 4. Pharmacological examples

Legend for Figure 4

Courtesy ref no-30-Current therapeutic targets for pharmacological treatment of NAFLD and NASH. There are no FDA-approved medications for patients with NAFLD/NASH so far. Currently, various pharmacological therapeutic candidates are being applied to the clinical trials. The illustration demonstrates the targeted pathway and phenotype for treatment of patients with NAFLD and NASH.

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TZD's work by controlling metabolic pathway by binding to the nuclear transcription factor Peroxisome Proliferator adenineActivated Receptor γ (PPAR γ) in addition to modulation of the expression of the target genes [86]. The genes possess a part in controlling glucose metabolism, storage of FA's along with adipocytes differentiation [87]. In agreement with this PPAR γ agonist escalated the expression of glucose transporter 4 (GLUT4alias SLC2A4) A as well as translocation, hamper TNFα as well as result in enhancement of insulin sensitivity in case of organs which are insulin sensitive [88]. Conversely T2D treatment effects increments of weight as an adverse action, since PPAR γ Receptor's are markedly expressed in adipocytes [89]. Enhancement of fat mass is restricted to the subcutaneous adipose depots instead of the visceral area [88,90]. That can be prevented by metformin therapy [91].

Recently it got documented that the PPAR γ agonist Pioglitazone possesses significant actions on NAFLD/NASH patients. In case of patients with NASH, it amelioratedliver fat collection along with fibrosis [92]. In case of patients with NASH in addition to T2DM, it results in reduction of hepatic steatosis, inflammation as well as serum alanine amino transferase (ALT) as well as aspartate amino transferase (AST) with better liver function [93]. In rodent models it decreases hepatic gluconeogenesis along with results in escalation of insulin sensitivity in the liver as well as other peripheral tissues [94].

Obeticholic acid (OCA); or INT-747; Farsenoid X receptor [FXR] agonist

Obeticholic acid (OCA) represents a Farsenoid X receptor [FXR] agonist, that is a nuclear receptor, with significant expression in the liver along with small intestine, having a significant part in the generation in addition to enterohepatic circulation of bile acids, besides controlling hepatic glucose as well as lipid metabolism, inflammation as well as lipoprotein constituents in addition to bile acid generation [95]. In rodent models OCA has anti-inflammatory along with, anti-fibrotic actions on HSC's as well as macrophages [96]. The transcriptional repressor small or short heterodimer partner (SHP), crossreacts with liver receptorhomolog1 (LRH1), that represents a positive controller of CYP7A1 which encodes for the rate limiting enzyme in the classic bile acids generation pathway as well as represses its ability for transcription [97]. HSC's getting exposed to FXR ligands escalated the expression of the transcriptional repressor SHP along with reduction of factors correlated with liver fibrosis [96]. Belief is that an FXR SHP controlling axis has a significant part in controlling liver fibrosis. OCA stimulation of FXR-action has 100 times greater potency in contrast to the chenodeoxycholic acid, that is a natural FXR agonist [98]. Escalation of insulin sensitivity results with the use of OCA in addition to, reduction of hepatic inflammation markers as well as fibrosis in patients with T2D as well as NAFLD [99].Weight reduction results in patients with NASH, with this weight reduction having extra advantageous actions on SerumALT/ASTamounts along with liver histology [100]. In addition to that it results in significant enhances fibrosis in patients with NASH [101]. It represents 1 of the agents holding maximum promise for NASH therapy, is in phase 3 trials [102].

Elafibranor (GFT-505; Peroxisome Proliferator Activated Receptor (PPAR)-agonist)

PPAR's represent transcription factors that get activated by ligand, belonging to the nuclear hormone receptors superfamily [103]. Their expression occurs in liver, adipose tissue (AT), heart, skeletal muscle, as well as kidney, besides controlling -β -oxidation along with gluconeogenesis [102]. Three kinds of nuclear receptor isoforms exist; PPARα, PPAR δ, as well as PPARγ. PPARα, facilitates β -oxidation, decreases triglycerides (TG), amounts, besides escalated high density lipoprotein (HDL) cholesterol amounts [104]. Further it hampers nuclear factor κB (NFκB) stimulation of inflammatory genes [104]. PPARα agonists like fibric acids derived compounds like fibrates is in usage widely for the treatment of hypertriglyceridemia, while it doesn't possess significant actions in NAFLD patients [105]. The reason for this is the existence of PPARα in a lot of organs besides liver. Akin to PPARα, PPAR δ causes escalation of FA oxidation along with decreases macrophages in addition to Kupffer cells activation, in view of its existence on macrophages [106]. GW50516 represents a synthetic PPAR δ particular agonist [107]. GW50516 can be thought of as attractive proposition in Clinical trials, in view of it possessing potent efficiency, however it possesses safety issues [108].

Elafibranor, alias GFT505 is a double PPARα as well as δ agonist [109]. It attenuates inflammation, apoptosis, necroptosis in case of NASH mouse model [110]. It led to reduction of histological hepatic steatosis, inflammation in addition to, robustness of fibrosis in both the NAFLD/NASH as well as fibrosis mouse model [111]. It has a tendency to result in weight reduction, but not that of liver in case of diet stimulated NAFLD/NASH rodent models [112]. In cases of obese subjects it enhances hepatic as well as peripheral insulin sensitivity [113]. Moreover it hampers proinflammatory (interleukin-1β, TNFα as well as F4/80), in addition to, profibrotic transforming growth factor beta TGF-β, tissue inhibitors of matrix metalloproteinase (TIMP2), collagen type1, alpha2 as well as collagen

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type1, alpha2 markers in obese subjects [114]. No -weight gain was reported [109,115]. Presently it is getting analysed in phase 3trials in NASH subjects [102].

Arachidylamido cholanoic acid (Aramchol) Stearoyl-Co A Desaturase (SCD1) Inhibitor

Aramchol represents the liver targeted, an innovative synthetic lipid molecule,a conjugate of the bile acid, cholic acid as well as arachidic acid (FABACs). It influences liver fat metabolism by causing reduction in FA generation along with escalation of β -oxidation [117]. Furthermore it results in stimulation of cholesterol efflux by activation of the ATP – binding cassette transporterA1 (ABCA1) [118]. Additionally, it decreases inflammation as well as fibrosis in methionine as well as choline deficient (MCD) fed mice [116]. Moreover it tends to ameliorate steatohepapititis as well as fibrosis by causing reduction in SCD1 amounts by controlling the transsulfuration pathway resulting in escalated glutathione amounts as well as the glutathione disulfide (GSSH/GDX redox couple for appropriate balance of redox environment [116].

In a phase 2 trial, of patients with NAFLD, Aramchol decreased the liver fat amounts along with liver histology [119]. No significant toxicity was observed as seen in circulating ALT as well as AST amounts, besides alkaline phosphatase (AP) amounts [119]. In view of it targeting general properties of NASH (like escalated liver fat amounts, lipotoxicity as well as OS) in addition to fibrosis Aramchol is at present getting generated for NASH treatment along with that of fibrosis. No significant alterations in body weight was observed in NASH patients. Phase 3 clinical trials are ongoing in patients with NASH as well as fibroses got started in 2019.

Liraglutide (GLP-1Agonist)

Glucagon like peptide 1 receptor (GLP-1) agonists have got well proven -in the form of attractive anti Diabetic agent in animals as well as - patients with T2DM [120]. GLP-1 represents an incretin hormone liberated from the L-cells in the distal ileum along with colon [121]. It causes stimulation of pancreas resulting in insulin generation, in addition to decreases glucagon generation [122]. Endogenous GLP-1 gets broken down by Dipeptidyl Peptidase-4 (DPP-4) enzyme within few minutes whereas Liraglutide possesses long half life 13h [123].

Exenatide that is a synthetic Extendin-4 was the 1st GLP-1R agonist that got FDA approval in 2005 for T2DM treatment in form of monotherapy or as add on therapy with metformin as well as or sulfonyl urea, in case control was not sufficient [124].

Liraglutide, the second GLP-1R agonist that got a license in 2010 by FDA for T2DM treatment. Further in 2020 it got FDA approval for therapy of obesity patients, dependent on its weight reduction advantages [125]. It possesses cardiovascular safety while treatment for weight reduction [126]. Anorexia secondary to Liraglutide is associated with glutamatergic POMC neurons, resulting in weight reduction [127]. In cases of NAFLD as well as NASH it causes reduction in liver fat amounts, besides with liver histology getting rectified along with normalization of enzymes (ALT as well as AST amounts) without deterioratrion of fibrosis [[128]. In view of rodent studies demonstrating Liraglutide conferred protection to pancreatic β cells from apoptosis via AKT modulated survival signaling [129]. It enhanced insulin sensitivity by activation of adenine monophosphate activated -protein kinase (AMPK) as well as decreases hepatic steatosis by modulation of lipid transportation, β-oxidation, DNL, as well as autophagy [130].

Selonsertib (ASK1 Inhibitor)

Balooning of hepatocytes, points towards the stimulation of the apoptosis pathway, which represents a hallmark of NASH along with fibrosis propagation [131]. Selonsertib represents -1ST in class Inhibitor of the apoptosis signal regulating kinase 1 (ASK1) [132]. Selonsertib hampers phosphorylation as well as activation of ASK1 by binding to the catalytic kinase domain of ASK1. It has been posited recently possessing therapeutic potential for fibrotic Diseases. In case of murine models, ASK1, that is a serine/threonine kinase, results in phosphorylation of p38 mitogen activated protein kinase (MAPK) as well as, resulting in activation ofc-Jun –N terminal kinase (JNK) resulting in activation of stress response pathways which exacerbate hepatic inflammation, apoptosis in addition to fibrosis [133]. In murine models of NASH, it significantly enhances besides hepatic steatosis in addition to fibrosis correlated with NASH, enhancement of cholesterol, the bile acid and lipid metabolism [133]. In phase 2 Clinical trials of NASH patients as well as stage 2-3 fibrosis, it has got demonstrated to avoid inflammation, fibrosis, escalated apoptosis as well as -propagation to cirrhosis [134]. Conversely, phase 3 Clinical trials of NASH patients along with advanced fibrosis were observed to escalate liver histology, but had no influence on fibrosis regression [135].

Simutuzumab (SIM;G6624)

Simutuzumab (SIM) represents a monoclonal Ab,that targets lysyl oxidase –like 2 (LOXL2) enzymatic activity which catalyzes the crosslinlinking of collagen in addition to elastin, resulting in remodeling of the extra cellular ma-

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trix (ECM) [136]. SIM binds TO LOXL2 as well as hampers its enzymatic action [137]. Hence it hampers the generation of growth factors that includes [connective tissue growth factor (CTGF]/CCN2) as well as TGFβ1 in addition to results in reduction of fibrosis [138]. In a mouse model possessing advanced fibrosis stimulated by NASH, SIM possesses an extra action in combination with the ASK1 Inhibitor [134]. Nevertheless, in phase 2b clinical trials of patients presenting with advanced fibrosis secondary to NASH it did not display any action on enhancement of fibrosis or cirrhosis that had been verified by hepatic collagen amounts [139].

C-C chemokine receptor CCR Dual -types -2 as well as 5 (CCR2/CCR5) antagonist -(cenicriviroc)

Liver inflammation is intricately correlated with chemokines responsible for controlling migration of hepatocytes as well as immune cells [140]. The C-C chemokine receptor 2 as well as 5 (CCR2, as well as -CCR5) with their associated ligands CCL2 as well as CCL3-5) have a correlation with the pathogenesis of Liver inflammation as well as fibrosis in the generation of [140,141]. CCR2 in addition to its ligand CCL2 escalated hepatic steatosis, macrophages collection, inflammation along with fibrosis [140]. Hepatic Stellate cells (HSCs) on activation, aid in fibrosis, liberate CCL5. CCL5 influences profibrotic action in hepatocytes through its receptor CCR5 as well as results in stimulation of lipid collection as well as proinflammatory factors [141].

CVC or cenicriviroc represents an innovative CCR2, as well as CCR5 antagonist which is at present in Clinical generation for the therapy of liver fibrosis patients presenting with NASH [142]. CVC results in reduction of markers of inflammation like IL-1β, IL-6 as well as influences antifibrotic actions [142]. Fast track movement was given by FDA in 2015, being a highly lucrative therapy for NASH as well as liver fibrosis. In a phase 2b study of NASH patients presenting with stage 2-3 fibrosis, CVC -demonstrated enhancement in liver fibrosis. In addition to no deterioration in -NASH [143]. At present a phase 3 clinicaltrial is ongoing for the therapy of NASH cases with liver fibrosis [144].

4.3 Diagnostic Approaches as well as Therapeutic Targets in NAFLD as well as - NASH – Adipocytokines

It is thought that NAFLD as well as NASH are secondary to lots of etiopathogenetic factors [78]. Of these we concentrate on adipokines liberated from adipose tissue (AT) which yield fatty acids (FA) as the main site aiding for NAFLD generation [45]. Various Adipokines are implicated in the pathogenesis as well as propagation of NAFLD [145]. Leptin, resistin, in addition to visfatin have a part in NAFLD generation as well as propagation of NASH [145,147]. Conversely adiponectin, irisin as well as ghrelin have advantageous actions on NAFLD as well as NASH [148,149]. Pharmacological drugs which impact liver histology along with pathophysiology might affect these adipocytokines amount. This points that adipocytokines could prove to be significant therapeutic targets as well as biomarkers in NAFLD robustness anticipation (Figure 5). These adipocytokines might further have a significant role in generation of HCC.

Adiponectin

Adiponectin is a significant Adipocytokines possessing the ability to hamper NAFLD generation. A reduction of circulating amounts of Adiponectin was found in cases of NAFLD as well as NASH [150]. They had an inverse association with the robustness of hepatic steatosis as well as inflammation. Pioglitazone, the antidiabetc which had a beneficial action on liver histology escalated adiponectin amounts, in patients withNASH [93]. Nevertheless, metformin the commonest used antidiabetc agent did not have any significant actions on either the liver histology but decreased the adiponectin amounts [89,151]. Vitamin E has a robust antioxidant action that can confer protection to bodies cells against Oxidative stress [152]. It had been thought to be an alternate medicine advocated for NAFLD as well as NASH. It enhances liver histology as well as displays certain adv actions in case of non Diabetes mellitus cases with NASH, as well as apparently it enhances adiponectin amounts [153]. Nevertheless, it has no efficacy in NASH cases with T2DM [153]. In case of mouse models, adiponectin represses hepatic lipid collection by lipid metabolism collection by escalated FA oxidation along with reduction in DNL [94]. Adiponectin has anti inflammation, anti fibrotic as well as anti apoptosis action [154]. Adiponectin delivery escalates hepatic steatosis along with inflammation [154]. Moreover adiponectin expression has an inverse association with tumor size as well as recurrence [155].

Leptin

Leptin is a hormone possessing appetite repression actions, that gets liberated from fat cells. It controls food consumption, body fat in addition to insulin sensitivity [156]. In animal models it is believed to escalate lipid metabolism in case of non AT's [157]. Nevertheless, in liver, it accelerates hepatic IR, that results in liver steatosis. Further it escalates -liver fibrosis [156]. Leptin delivery might

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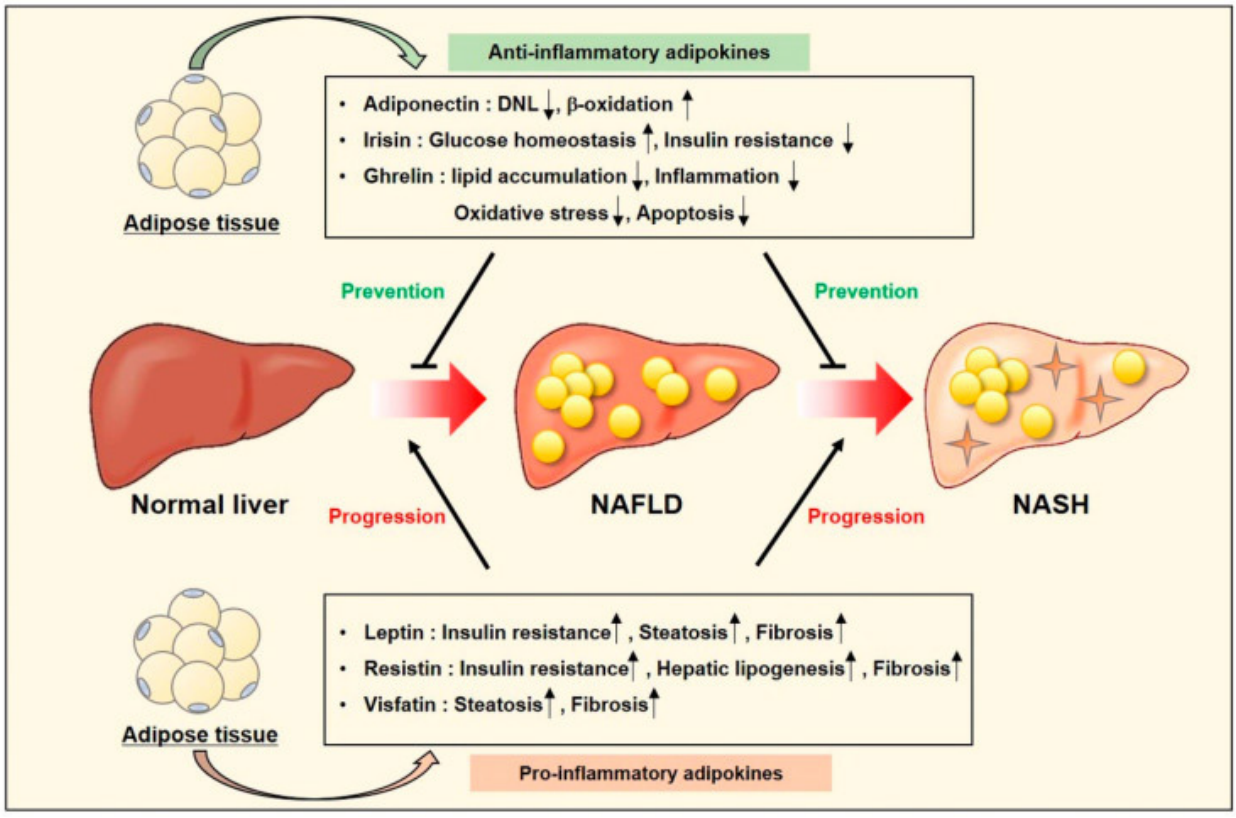

Figure 5. NAFLD robustness anticipation

Legend for Figure 5

Courtesy ref no-30-Adipokines as diagnostic markers and therapeutic targets in NAFLD and NASH. Adipokines that are secreted from adipose tissues are classified into anti-inflammatory adipokines and pro-inflammatory adipokines. Anti-inflammatory adipokines including adiponectin, irisin, and ghrelin inhibit the development and progression of NAFLD and NASH, whereas pro-inflammatory adipokines including leptin, resistin, and visfatin promote the development and progression of NAFLD and NASH.

escalate proinflammatory along with fibrogenic reaction in the liver through procollagen 1 along with transforming growth factor beta (TGF-β1) [158]. Nevertheless, in humans its actions are not certain. Escalated circulating amounts are present in patients with NASH [159]. Leptin expression has a positive association with robustness of steatosis, inflammation along with fibrosis [160]. Leptin expression has a positive association with cell proliferation in HCC, as validated by proliferation marker Ki67 [133].

Resistin

Resistin is a proinflammatory adipocyte obtained modulator of hepatic IR [161]. Further it gets expressed in liver as well. It is correlated with hepatic lipogenesis as well as liver fibrosis [162]. Circulating Resistin amounts are escalated in patients with NAFLD as well as NASH, with circulating Resistin amounts in NAFLD patients are associated with the robustness of steatosis, inflammation along with fibrosis [162]. Escalated Resistin amounts are believed to be correlated with IR. In subjects with NAFLD Pioglitazone therapy escalates insulin sensitivity along with reduces plasma Resistin amounts [163].

Ghrelin

Ghrelin represents an anti-inflammatory Adipokine. It is the endogenous ligand for growth hormone secretagogue receptor possessing a peptide structure having 28 amino acids [164]. In patients with NAFLD lesser Ghrelin are correlated with IR [165]. Plasma Ghrelin amounts possess a significant association with liver function. Nevertheless, Ghrelin amounts are not influenced by Pioglitazone in the form of one of insulin sensitizers [43]. At the time of as well as following NAFLD generation, Ghrelin delivery escalates lipid metabolism, inflammation, Oxidative stress as well as apoptosis [166]. In mouse models Ghrelin resulted in reduction in TG amounts as well as the cytokines TNF-α, IL-6 as well as ameliorated lipotoxicity via autophagy activation in addition to hampering NFκB [167]. In toto Ghrelin might work as a biomarker for both diagnosis and management of non alcoholic fatty liver disease.

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Irisin

Irisin is a myokine liberated from skeletal muscles on shivering in addition to exercise stmn [168,169]. Fibronectin typeIII domain containing 5 precursors (FNDC5) is the precursor of Irisin. FNDC5/Irisin facilitate thermogenesis in AT via ERK as well as p38pathways [170]. It causes enhancement of glucosehomeostasis along with IR, besides resulting in weight [171] reduction. In the recent past FNDC5/Irisin induction was obtained at the time of adipocytes differentiation, as well as can get over liberated from human visceral (VAT) as well as subcutaneous (SAT) adipose tissue [172]. It is believed to be a compensatory action. In agreement with this circulating Irisin amounts are escalated in NAFLD patients, besides being positively associated with portal inflammation [173], that is further thought to be a compensatory action.

Visfatin

Visfatin represents an inflammatory adipokine enzyme (alias nicotinamide phospho ribosyl transferase as well as pre B cell colony enhancing factor). Visfatin amounts are escalated in T2DM in addition to insulin resistant situations [174]. Circulating Visfatin amounts are further escalated in NAFLD patients, besides being correlated with hepatic steatosis as well as fibrosis [175]. Nevertheless, they don't get influenced by insulin sensitizers like pioglitazone, rosiglitazone as well as metformin [176].

4.4 NAFLD as well as - NASH --Obtained HCC

Pathogenesis of NAFLD as well as - NASH --associated -HCC

HCC being the 3rd commonest etiology of cancer associated mortality [177]. NAFLD as well as NASH associated HCC represents the most rapidly escalated indication for liver transplantation [178]. Cirrhosis exists in about 60% of cases of NAFLD as well as NASH associated HCC [178]. This points that HCC can get stimulated from NAFLD as well as NASH without cirrhosis. Hence belief is that inflammatory parameters will also have a key part in NAFLD/NASH-obtained HCC.

Gut obtained endotoxin

Already detailed how Gut obtained endotoxins work in the form of alternative inflammatory parameters have a significant part in the generation of NAFLD/NASH. The amounts of LPS, alias endotoxins are further escalated in portal as well as peripheral venous veins of patients with HCC [179]. They facilitate significantly the invasion potential besides inducing epithelial –mesenchymal transition (EMT), despite them hampering tumor growth as well [180]. LPS stimulates JNK in addition to MAPK through TLR4 in HCC cells while hampering of JNK in addition to MAPK causes a significant reduction in EMT taking place [180]. Hence the LPS-TLR4 signaling might be one of the lucrative pathways in controlling the propagation from NAFLD-NASH to HCC [181].

Adipokines

Adipokines represent inflammatory parameters associated with HCC generation. Expression of adiponectin in human HCC has an inverse association with the tumor size [182]. It escalates phosphorylation of c-jun N terminal kinase (JNK) as well as activation of caspase 3 resulting in apoptosis in HCC [182]. Hampering of JNK phosphorylation avoids anti apoptotic actions of adiponectin [182]. Adiponectin has a chemoshielding, besides hepatoshielding actions through sulfatase2 (SULF2) in HCC [183]. Adiponectin deletion facilitates fibrosis as well as HCC propagation in a choline deficient NASH mouse model [184]. Conversely high amounts of circulating adiponectin makes it feasible to anticipate the subsequent generation of HCC along with poor HCC survival [185]. Moreover adiponectin hampers the oncogenic action of leptin on cell proliferation, migration as well as invasion of HCC [155].

Leptin expression is escalated in hepatoma tissues as well as cell lines [186]. Regulatory T Cells(TRegs), effector CD 4+T cells, as well as CD 8+T cells result in stimulation of the expression of the Leptin receptor (LEPR) in the liver following generation of HCC [186]. Macrophages as well as, dendritic cells, upregulate LEPR expression on the T Cells. Leptin hampers activation of TRegs as well as function [186]. Escalated Leptin expression in HCC is correlated with the expression of human telomerase reverse transcriptase (hTERT) [187]. Leptin might possess a key part in obesity associated tumorigenesis. Adipokines that include adiponectin along with Leptin are critical actors in obesity associated conditions as well as might be implicated in the etiopathogenesis of NAFLD as well as HCC.

Diagnostic as well as - -Therapeutic target in NAFLD as well as - NASH --Obtained HCC-Hepatokines

The liver is an organ which liberates cytokines, known as hepatokines. Adipose tissue (AT) in NAFLD, having the properties of hepatic TG collection, has a key part in facilitation of FFA uptake into the liver via lipolysis [45]. Hence the part of adipokines from AT, that yields energy source for the generation of NAFLD, would be very significant in the liver. Conversely, lipid droplets collection by itself does not influence inflammation as well as is believed to be simple steatosis. The propagation from NAFLD to NASH to HCC needs extra factors

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like oxidative stress, mitochondrial impairment as well as endoplasmic reticulum (ER) Stress [63,188]. Another significant factors facilitating NASH in simple steatosis is free nonesterified cholesterol as well as its oxidized products [189]. They are cytotoxic, influencing synergistic actions with TNF, that is markedly escalated in NASH patients [189]. Hence hepatokines liberated from liver might have an impact of potency in the propagation of NAFLD to NASH to HCC (Figure 6) greater propagation.

α2-HS- glycoprotein (Fetuin A as well as - Fetuin B)

Fetuin A, that is one of the liberated glycoproteins is believed to be the 1st hepatokine demonstrated to be correlated with metabolic diseases [190]. Fetuin A gets positively correlated with hepatic steatosis as well as IR1 [191]. Its amounts are escalated in patients with NAFLD, NASH in addition to T2DM [192]. In the form of a significant source of NAFLD generation, FFA escalates proinflammatory Fetuin A expression [24]. FFA stimulated Fetuin A works as an endogenous ligand of TLR4, as well as accelerates lipid modulated insulin resistance [193]. FFA can further escalate the recruiting of NFκB to the Fetuin A promoter as well as escalate the generation as well as liberation of Fetuin Ain primary hepatocytes [194]. Pioglitazone significantly represses serum Fetuin A amounts in patients with T2DM [195]. Pioglitazone hampers mRNA as well as protein amounts of hepatic Fetuin A along with oral delivery of pioglitazone in mice partly mitigated IR with reduction in hepatic Fetuin A expression [196]. These data point that Fetuin A might serve as a therapeutic target of NAFLD/NASH as well as IR. Moreover circulating Fetuin A amounts are escalated in patients with HCC [197]. Fetuin B -might also work out to be an independent pointer of NAFLD generation [198]. It also stimulates hepatic steatosis, IR, glucose intolerance [166,199]. It results in phosphorylation amounts as well as exacerbates LXR/SREBP1c modulated hepatic lipogenesis [200]. Conversely, circulating Fetuin A as well as circulating Fetuin B amounts in NAFLD patients have a negative correlation with liver fibrosis [201].

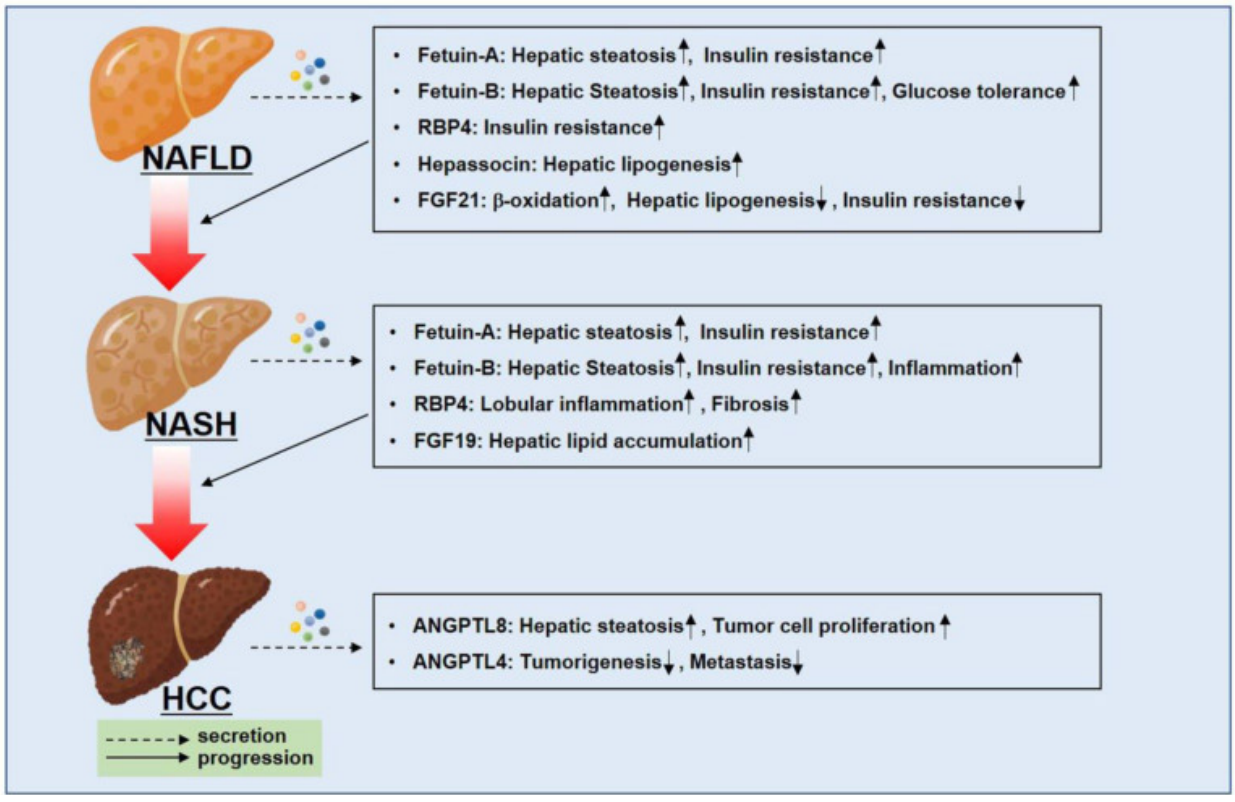

Figure 6. the propagation of NAFLD to NASH to HCC

Legend for Figure 6

Courtesy ref no-30-Hepatokines that are secreted from the liver are closely associated with the progression from NAFLD to NASH to HCC. Hepatokines including Fetuin-A, Fetuin-B, RBP4, and FGF19 play an important role in NAFLD and NASH. They are associated with hepatic lipid accumulation, insulin resistance, and inflammatory signaling pathways. Additionally, ANGPTL4 and 8 tend to function in opposite ways in HCC tumorigenesis.

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Retinol Binding protein-4 (RBP4)

The liver has a central part in Vitamin A metabolism. In NAFLD hepatic Vitamin A homeostasis gets disturbed [202]. RBP4 is a particular Retinol/Vitamin A carrier protein liberated from the liver. Further it also gets liberated from adipocytes along with macrophages [203]. Serum RBP4 amounts are correlated with NAFLD generation [204]. Circulating RBP4 amounts have a positive association with body mass index (BMI) as well as IR [205]. In case of moderate to severe NASH, escalated amounts of RBP4 was association with lobular inflammation in addition to fibrosis scores [206]. In case of cirrhosis, expression of RBP4 escalated hepatic glucose generation, but not insulin sensitivity [207]. One knows that Vitamin A homeostasis is impaired in addition to decreased secondary to liver fibrosis as well as cirrhosis. Significantly escalated amounts of RBP4 might become a marker for NAFLD generation, along with the lower amounts of RBP4 might further be a marker for propagation of NASH with fibrosis in NAFLD stages [204].

Hepassocin (HPS)

Hepassocin is a hepatocyte obtained fibrinogen correlated peptide (HFREP-1), a hepatokine which is implicated in during liver regeneration [208]. In case of mice along with human patients with NAFLD, plasma HPS amounts are escalated [209]. Overexpression of hepassocin escalated hepatic lipid collection, besides NAFLD activity scores (NAS), while its removal enhances them [209,210]. Serum HPS amounts are escalated with the amounts of inflammatory cytokines in addition to lipogenic gene expression [210]. HPS stimulated hepatic steatosis gets triggered via the extracellular signal regulated kinase (ERK1/2)-based pathway [210]. FFA stimulates expression of HPS [211,212]. Oleic acid the maximum distributed unsaturated fatty acids, stimulates expression of HPS vis the Signal Transducers and Activators of Transcription3 (STAT3) signaling [211]. Palmitate, that has the maximum content of saturated fatty acids, stimulates expression of HPS via endoplasmic reticulum (ER) stress – modulated p38 activation by C/EBPβ in primary hepatocytes [212]. In addition to that hepatic expression of HPS gets escalated by partial hepatectomy in mice, as well as gets stimulated by hepatic nuclear factor 1(HNF-1α) via the IL-6/STAT3 pathway [213]. Delivery of HPS confers protection against liver damage as well as escalates survival in rats with hepatitis [214]. Liver particular expression of HPS gets suppressed with the downregulation of the correlation of HNF1 alpha with reduced amounts of hepassocin in human Hepatocellular carcinoma [213,215].

Fibroblast -growth -factor 19 and -21 (FGF19 as well as - - FGF21)

FGF19 as well as FGF21 belong to the FGF19 family, which needs the Klotho proteins as cofactors. They stimulate FGFR4 along with Klotho, that has an abundance of expression in hepatocytes [216]. FGF19 as well as FGF21 have the role of controlling glucose, lipid as well as bile acid metabolism [217].

Fibroblast -growth -factor 19 (FGF19)

In case of NASH, the amounts of serum FGF19, Fibroblast growth factor receptor 4(FGF R4), along with bile acids are significantly escalated, that causes dysfunction of FXR as well as FGFR4 modulated signaling [218]. In cases of NASH, FAF analogue significantly causes reduction in hepatic lipid accumulation. Conversely up regulation of FGF19 is correlated with the propagation, recurrence, in addition to worst prognosis of HCC [219]. The β- Klotho proteins are further escalated in liver as well as serum of subjects with HCC [220].

Fibroblast -growth -factor 21 (FGF21)

The hepatokine FGF21 possess advantageous actions on hepatic lipid metabolism. It escalates lipid oxidation, represses DNL, in addition to escalate insulin resistance by inhibiting mammalian target of rapamycin complex1 (mTOR) [221]. Hepatic FGF21 expression possesses a positive association with adipocyte in addition to intra hepatic TG, with its serum amounts being escalated by significant amounts in subjects with obesity, NAFLD as well as T2DM [222]. Serum amounts of FGF21 are escalated in obese children with or without NAFLD [223]. Escalated amounts of FGF21 are believed to be based on the robustness of steatosis, along with positive association with NAS [224]. Cases of advanced NASH can be labelled on the basis of properties of circulating FGF21 amounts in combination with inflammatory factors (cytokeratin 18, M30antigen, IL-1Ra, pigment epithelium-based factor, as well as osteoprotegrin) [225]. Enhancement of serum as well as hepatic FGF21 amounts are seen in cirrhosis as well as HCC [226].

Angiopoietin –Like Protein- 8 (betatrophin/ ANGPTL8)

ANGPTL8/betatrophin represent a circulating hepatokine also called TD26 as well as lipasin [227]. It is significantly expressed in liver as well as visceral adipose tissue (VAT) [228]. Over expression of ANGPTL8 in brown adipose tissue (BAT) escalates lipoprotein lipase (LPL)

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action along with TG uptake [168,229] [reviewed by us in 169]. Serum ANGPTL8 are significantly escalated in patients with pre Diabetes as well as type2 Diabetes [230]. It has been documented that ANGPTL8 is not implicated in Pancreatic βcells expansion, although it has a part in controlling glucose along with lipid metabolism in mice [231,232]. In addition ANGPTL8 expansion is significantly escalated in HCC [228]. It crosstalks with SREBP1, secondary to which it facilitates lipogenesis along with tumor cell proliferation in HCC [228]. Hence it is believed that it has a positive association with the tumor size. ANGPTL8 needs ANGPTL 3 instead of controlling LPL by itself [229,233]. ANGPTL 3 controls TG metabolism by directly hampering LPL [229,233]. ANGPTL 4 gets markedly expressed in liver as well as adipose tissue, in addition to can controls TG metabolism by hampering LPL action [229,235]. Nevertheless, ANGPTL 4 expression reduction exists in HCC, besides Over expression of ANGPTL4 hamper hepatocarcinogenesis along with metastasis of HCC [236].

5. Conclusions

Over the past 2 decades the percentage of HCC cases possessing non viral etiology has been escalating at a fast pace. Secondary to this the significance of NAFLD/NASH obtained HCC has been showing up. At present what holds the truth is that management of subjects with NAFLD/NASH is usually carried out with the utilization of medicines for the treatment of type2 Diabetes mellitus as well as hyperlipidemia. The adverse actions which show up following the long term utilization have to be taken into account. Hence proper therapeutic targets along with FDA approved treatments are required at war footing. It is believed that the causation of failure of generation of a therapy for subjects with NAFLD/NASH in spite of continuous attempts are i) pathogenesis is still not totally clear; ii) absence of actions; iii) safety issues. Adipose tissue as well as the liver constitute the most significant organs that are correlated with lipid metabolism. Hence it is essential to watch adipokines as well as hepatokines that can work as diagnostic in addition to therapeutic targets as well as signaling pathways that get targeted by the present therapies. In addition, to that it needs to get deep insight via the classification as per the etiology of NAFLD. It would yield a significant point of view for the regulation of the metabolic phenotype from NAFLD to NASH to HCC. At present it has been accepted that think of NAFLD as being occurring secondary to a concert of different parameters that include nutritional factors, Gut Microbiota, genetic in addition to epigenetic factors as well as adipokines in addition to hepatokines. To be able to achieve a successful therapy, it is essential to watch different factors in a wider perspective.

References

[1] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Kochar Kaur -K,Allahabadia GN,Singh M(2016). An update on Aetiopathogenesis and management of Obesity.Obes Control Ther3(1):1-17. Diabetes Res Clin Pract 2014;103:137-49.

[2] Kochar Kaur -K,Allahabadia GN,Singh M(2013) Current management of obesity in an infertile female. Recent Advances -and Future Prospectives.Drugs J Pharm Nutr Soc;3:1-13.

[3] Kochar Kaur -K,Allahabadia GN,Singh M .Therapeutic Utilization of Neuro Imaging Studies in Obesity for Optimal Utilization of Drugs used in Treatment for Obesity-Lessons Learnt from Bariatric Surgery. -J Ageing Restor Med (JARM)n2019;2(2):89-97.

[4] Kochar Kaur -K,Allahabadia GN,Singh M . Existing and prospective pathways for intervention in treatment of obesity in a novel way-a review; -*MOJ Drug Des Develop Ther.* 2018;2(3):95-105. DOI: 10.15406/mojddt.2018.02.00035.

[5] Kochar Kaur -K,Allahabadia GN,Singh M .Advances in BAT physiology for understanding and translating into Pharmacotherapies for obesity and comorbidities. *MOJ Drug Des Develop Ther.* 2018;2(5:166-176.

DOI: 10.15406/mojddt.2018.02.00057.

[6] Kochar Kaur -K,Allahabadia GN,Singh M. Targeting macrophage polarization for therapy of diabesity–the feasibility of early improvement of insulin sensitivity and insulin resistance-a comprehensive systematic review. J Diab Metab Disorder Control. 2021;8(1):6-25.

[7] Kochar Kaur -K,Allahabadia GN,Singh M. Are we at the verge of finding a new efficacious pharmacotherapy for obesity in the form of agonism at triple drug receptors: glucagon, Glucagon like peptide1 (GLP1), glucose dependent insulin tropic peptide (GIP). *MOJ Drug Des Develop Ther.* 2019;3(1):22-27.

[8] Kochar Kaur -K,Allahabadia GN,Singh M. Targeting Orexin Neurons for Treatment of Obesity is It Feasible in Human Being-A Systematic Review. Journal of Neurology Research Reviews & Reports. J Neurol Res Rev Rep, 2019; 1(1): 1-9.

[9] Kochar Kaur -K,Allahabadia GN,Singh M .Importance of simultaneous treatment of obesity and diabetes mellitus: A sequelae to the understanding of diabesity-A review.*Obes Res Open J*. 2019; 6(1): 1-10. DOI: 10.17140/OROJ-6-136.

[10] Kochar Kaur -K,Allahabadia GN,Singh M . Role of

Adipocyte Impairment in Heart Failure Induction in Subjects that are Obese along with Prediabetes and Overt Diabetes Mellitus - A Systematic Review. International Journal of Cardiology and Cardiovascular Disorder2021; 2(1) :1-21.

[11] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. A Mini Review on Development of Newer Therapies for Non Alcoholic Fatty Acid Liver Disease with Emphasis on Vitamin D and its Receptor and Allyl Isothiocyanate (AITC)". Acta Scientific Nutritional Health 2019; 3(12) :1-5.

[12] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An Update on Further Progression of NAFLD, NASH with Prospective Therapies Like L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, as well as Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin as Alternatives. Int J Clin Med Cases. 2020 Jan;3(3):138.
DOI: 10.31021/ijcmc.20203138-29/1/2020 jan 29.

[13] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Have Probiotics and Synbiotics passed the test of time to be implemented in management of obesity and related metabolic disorders-a comprehensive review. *Adv Obes Weight Manag Control*. 2019;9(1):21-28.
DOI: 10.15406/aowmc.2019.09.00269.

[14] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Will Probiotics Provide the Answer for Therapy of Non-alcoholic Fatty Liver Disease (NAFLD)? – A Systematic Review. Biochem Physiol -2020;9: 257.

[15] Kulvinder Kochar Kaur,Allahbadia GN,Singh M.. Rosmarinic Acid-A New Hope for Liver Diseases Like Cirrhosis, Hepatocellular Carcinoma-NeedsTranslation to Humans". EC Endocrinology and Metabolic Research 2019;4(6): 289-301.

[16] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How do we apply advances in knowledge of Hepatic Macrophages in treating Liver Diseases especially non alcoholic -fatty liver disease(NAFLD), non alcoholic steatohepapititis(NASH), with the increasing incidence of Diabesity-A Systematic Review.EC Endocrinology and Metabolic Research published in2020.

[17] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Mechanisms that associate extension of Nonalcoholic fatty liver diseases(NAFLD) to NASH (Nonalcoholic steatohepatitis) and further progressing to cirrhosis and Hepatocellular carcinoma(HCC) in addition to few proposed biomarkers for poor prognosis.J Gynaecol 2021;1(16):1-18.

[18] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How can we optimize therapy of Non Alcoholic Fatty Acid Liver Disease-A Short Communication on role of Astragaloside IV and other prospective agents". Clinical Research and Clinical Case Reports, 2021;1(3):1-4;
DOI: http;//doi.org/04.2021/1.1013.

[19] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Paradoxical Additional Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection-A Minireview". *Acta Scientific Gastrointestinal Disorders* 4.7 (2021): 15-26.

[20] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. 'An update on management of Nonalcoholic Fatty Liver Disease &Nonalcoholic Steatohepapititis-Is -the time ripe for achieving -resolution of NAFLD &NASH soon''.2021Under review.

[21] Khan MAB,Hashim MJ,King JK,Govender RD,Mustafa H,AlKaabi J. -Epidemiology of type2 Diabetes mellitus- Global burden of disease and forecasted trends.J Epidemiol Glob Health 2020;10:107-11.

[22] Masmiquel L,Leiter LA,Vidal J,Bain S,Petrie J,-Franek E,etal.LEADER 5: Prevalenceand cardiometabolic impact ofobesity in cardiovascular high risk patients with type2 Diabetes mellitus:baseline global date from the LEADER trial. Cardiovasc Diabetol 2016;10:29.

[23] Ng ACT,Delgado V,Borlaug BA,Bax JJ.Diabesity :the combined burden of obesity -and Diabetes on heart disease and the role of imaging .Nat Rev Cardiol 2021;108:291-304.

[24] Gonzalez-Gross M,Melendez A.Sedentarism,active lifestyle and sport:impact on health and -obesity prevention.Nutr Hosp2013;5:89-98.

[25] Younossi ZM .Nonalcoholic fatty liver disease a global public healthperspective. J Hepatol 2019.;70: 531-44.

[26] Sunny NE,Bril F,Cusi K. Mitochondrial Adaptation in non alcoholic -fatty liver disease:novel mechanisms and treatmentstrategies. Trends -Endocrinol Metab 2017; 28:250-60.

[27] Abd-El-Khader SM, El-Den Ashwamy EM. Nonalcoholic fatty -liver disease:the diagnosis and management. World JHepatol 2015; 7:846-58.

[28] Arulanadan A,Loomba R.Non invasing testing -for NASH and NASH with advanced fibrosis:are we there yet?Curr Hepatol Res 2015;14: 109-18.

[29] Chalasani N, Younossi ZM, Lavine AE,Charlton M, Cusi K, RinellaM, -etal .The diagnosis and management of - non alcoholic fatty liver disease: practice

  DOI: https://doi.org/10.30564/jer.v3i2.3520

guidance from the -American -Association for thestudy of - Liver disease. -Hepatology -2018;67: 328-57.

[30] Kim H, Lee DS,An TH,Park HJ,Kim WK,Bae KH,Oh KJ.Metabolic spectrum of liver failure in type2 - Diabetes and obesity:From NAFLD to NASH to HCC.Int J Mol Sci 2021;22:4295.

[31] Mahjoubin-TehranM,DeVentisA.Mikhailidis DP,Atkin SL,Mantzoros CS,Jamialahmadi T, -etal . Nonalcoholic fatty liver disease and steatohepatitis:state of the art on effective therapeutics based on the gold standard method for diagnosis. Mol Metab 2020;13:101049.

[32] Loomba R.Adams LA.The 20% rule of NASHprogression:the natural history of -advanced fibrosisand cirrhosis caused by NASH. Hepatology 2019;70: 1885-88.

[33] Wong SW,Ting YW,Chan WL. Epidemiology of -non alcoholic fatty liver disease related Hepatocellular carcinoma and its implications.JGH Open 2018;2: 235-41.

[34] BenhammouJN,Lin J,Hussain SK, El-Kabany M.Emerging risk factors for non alcoholic fatty liver disease - -associated Hepatocellular carcinoma. Hepatoma Res -2020;6:35.

[35] Huang DQ,El-SeragHB, Loomba R. Global Epidemiology of NAFLD- related HCC:Trends ,predictions,riskfactors and prevention. Nat Rev -Gastroenterol -Hepatol 2021;18:223-38.

[36] Anstee QM,McPherson S,Day CP.How big a problem -is Nonalcoholic fatty liver disease?BMJ2011;343:d3897.

[37] Tomah S,Alkhoury N,Hamdy O. Nonalcoholic fatty liver disease and type2 Diabetes:where do Diabetologists stand? Clin Diabetes Endocrinol 2020;6:9.

[38] Jarvis H,Craig D,Barker R,Spiers G,Stow D, Anstee QM, -etal .Metabolic risk factors -and incident advanced liver disease in Nonalcoholic fatty liver disease(NAFLD) :a systematic review and -meta-analysis of -population -based observational studies.PLoS Med 2020;17:e1003100.

[39] Miya narsky L,Manchem Y,Shibolet O. Treatment of Hepatocellular carcinoma:steps forward but but still a long way to go. World JHepatol 2015; 7:566-74.

[40] Goto K,Roca Suarez AA,Wrench F,Baumert TF,Lupberger J.Virus and Hepatocellular carcinoma:when the host loses its grip. Int J MolSci 2020;21):3057.

[41] Enomoto H,Ueno Y,Hiasa Y,Nishikawa H,Hige S,Taki kawa Y, -etal .Japan etiology of LiverCirrhosis Study Group in the 54th annual meeting of JSH.The transition in the -etiologies of -Hepatocellular carcinoma-complicated LiverCirrhosis in anationwide survey of Japan.J Gastroenterol -2021;56:158-67.

[42] Kinoda T, Goto K,Hirotsu Y,Masuzaki R,Moriyama M,Omata M. Molecular mechanisms :connections -between Nonalcoholic fatty liver disease, steatohepapititis and Hepatocellular carcinoma. Int J MolSci 2020;21):1525.

[43] Kim WK,Bae KH, Lee SC,Oh KJ.The latest insights into adipokines in -Diabetes. J Clin Med - - 2019; 8:1874.

[44] David Hojland L,Kykkesfeldt J,Tveden Nyborg . Molecular mechanisms of hepatic lipid accumulation in Nonalcoholic fatty liver disease. Cell Mol Life Sci -2018;75: 3313-327.

[45] Donnelly KL,Smith CI,Schwazenberg SJ,Jessurun J,Boldt MD,Parks EJ.Sources of fatty acids stored in liver and secreted via lipoprotein in patients with - non alcoholic fatty liver disease. J Clin Invest 2005;115:1343-51.

[46] Michele AB, David EC. Triglyceride metabolismin the liver .Compr Physiol -2017;8: 1-8.

[47] Draison F,Moulin P,Beylot M.Contribution of -hepatic Denovo lipogenesis and resterification of plasma non esterified fatty acids to plasma Triglyceride synthesis in Nonalcoholic fatty liver disease. Diabetes -Metab -2003;29:478-85.

[48] Chiu S,Mulligan K,Schwartz JM.Dietary arbohydrate and fatty liver disease: Denovo lipogenesis. Curr -Opin Clin Nutr Metab Care 2018;21:277-82.

[49] Linden AG,LiS,Choi HW,Fang F,Fukasawa U, Ueda K, -etal .Interplay between ChREBP and SREBP1c coordinates -postprandial glycolysis and lipogenesis -in livers of mice.J Lipid Res -2018;59: 475-87.

[50] Day CP,James OF. Steatohepapititis:A tale of two hits? Gastroenterology 1998;114:842-45.

[51] Arrese M,Cabrera D,Kalergis AM,Feldstein AE. Innate immunity and inflammation in NAFLD/ NASH. Dig Dis Sci 2016;61:1294-1303.

[52] Fukut H.Gut- liver axis in liver cirrhosis :how to manage leaky gut and endotoxaemia. World J Hepatol 2015; 7:425-42.

[53] JuC,Tacke F. Hepatic Macrophages in homeostasis and -liver diseases:from pathogenesis to novel therapeutic strategies. Cell Mol Immunol 2016;13: 316-27.

[54] Chakaroun RM,Massier L,Kovacs P.Gut microbiome, intestinal permeability - and tissue bacteria in metabolic disease:perpetrators or bystanders? Nutrients -2020;12:1082.

[55] Carpino G,Del Ben M,Pastori D,Carnevale R,Baratta F,Overi D, -etal .Increased liver localization of lipo-

 DOI: https://doi.org/10.30564/jer.v3i2.3520

polysaccharides in human and experimental NAFLD. Hepatology 2020;72: 470-85.

[56] Harte AL,Da Silva NF,Creely SJ,McGeeKC,Billyyard T,Youssef-Elabd EM, -etal .Elevated endotoxin levels in non alcoholic fatty liver disease.J Inflamm2010;7:15.

[57] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761-72.

[58] Kudo H,Takahara T,Yata Y,Kawai K,Zhang W,Sugiyama T. Lipopolysaccharides triggered TNFα-induced apoptosis in murine model of non alcoholic steatohepapititis model.J Hepatol 2009;51:168-75.

[59] Ma J,Zhou Q,Li H. Gut microbiota and Nonalcoholic fatty liver disease:insights on mechanisms and therapy. Nutrients -2017;9:1124.

[60] Jin C,Engstler AJ,Ziegenhardt D,Bishoff SC,Trautwein C.Bergheim I.Loss of -lipopolysaccharides binding protein attenuates -the development of diet induced - non alcoholic fatty liver disease in mice.J Gastroenterol Hepatol -2017;32:708-15.

[61] Lawrence T.The nuclear factor κB pathway in inflammation.Cold Spring HarbaPerspect Biol 2009;1:a001651.

[62] Lancaster GI,Langley KG,Berglund NA,Kammoun HL,Reibe S,EstevezE, et al.Evidence that TLR4 is not a receptor for saturatedfatty acids but mediates lipid-induced inflammation by reprogramming -macrophagemetabolism. Cell Metab 2018;27:1096-110.

[63] Sumida Y,Yoneda M.Current -and future Pharmacologic therapies for NAFLD/ NASH. J Gastroenterol -2018;27:1096-110.

[64] Masarone M,RosatoV,DallioM,Gravina AG,Aglitti A,LoguercioC, et al.Role of Oxidative stress in the pathogenesis of NAFLD. Oxid Med Cell Longev -2018;2018:9547613.

[65] Simoes ICM,Fontes A,Pinton P,Zischka H,WieckowskiMR. Mitochondria in non alcoholic fatty liver disease. Int J Biochem Cell Biol 2018;95:93-99.

[66] Serfaty L,Lemoine M.Definition and natural history of metabolic steatosis: Clinical aspects of NAFLD, NASH and cirrhosis. Diabetes -Metab -2008;34:634-37.

[67] Palmieri B,SblendorioV. Oxidative stress detection:what for ?Part II.Eur Rev Med Pharmacol Sci2007;11:27-54.

[68] Forrester SJ,Kikuchi DS,Hernandes MS,XuQ,Griendling KK. Reactive oxygen species in Metabolic -and -inflammatorysignaling.Circ Res 2018;122:877-902.

[69] Chen Z,Tian R,She Z,Cai J,LiH. Role of Oxidative stress in the pathogenesis of NAFLD.. Free Rad Biol Med -2020;152:116-41.

[70] Thuy LTT,Hai H,Kawada N.Role of cytoglobin ,a novel radical scavenger -in stellate cell activation and hepatic fibrosis -.Clin Mol Hepatol 2020; 26:280-93.

[71] Ilyasova D,Scarborough P,Spasojevic I.Urinary biomarkers of Oxidative stress. Clin Chim Acta 2012;7:219-27.

[72] Damiano S,Sozio C,La Rosa G,Santillo M.NOX dependent signaling dysreulation in severe COVID -19. Clues to effective treatment.Front -Cell Inf -Microbiol -2020; 10:608435.

[73] Angelico F,Loffredo L,Pignatelli P,Augelletti T,Carnevale R,Pacella A, et al. Weight loss is associated -with -improved endothelial dysfunction via NOX2 –generated Oxidative stress down regulation in patients with Metabolic Syndrome.Intern Energ -Med -2012;7:219-27.

[74] Del Ben M,Polimeni L, Carnevale R,Bartimoccia S,Baratta F,Nocella C, et al. NOX2 –generated Oxidative stress is associated -with - severity of ultrasound -liver steatosis - inpatients with -non alcoholic fatty liver disease.BMC Gastroenterol -2014;14:81.

[75] Dong Y,Yuan Y.Accelerated inflammation and Oxidative stressinduced by LPS in acute lung injury.:inhibition by ST1926. Int J Mol Med -2018;41(5):3405-21.

[76] Loffredo L,Zicani AM,Perri L, Carnevale R,Nocella C, Angelico F, et al.Does Nox2 over activation in children with Nonalcoholic fatty liver disease? Antioxid -Redox Signal -2019;30:1325-330.

[77] Kim SY, Jeong JM,Kim SJ,Seo W, Kim MH,Choi WM, et al. Proinflammatory Hepatic Macrophages generate ROS -through NADPH-oxidase -via endocytosis of -monomeric - TLR4-MD2 complex.Nat Commun2017 ;8:2247.

[78] Buzzzetti E, Pinzani M, Tsochatzis EA . The multiple hit pathogenesis of Nonalcoholic fatty liver disease (NAFLD). Metab Clin Exp 2016; 65: 451-64.

[79] Chalasani N, Younossi ZM, Lavine AE, Diehl AM,Brunt EM,Cusi K, et al. American Gastroenterological - Association, American -Association for thestudy of - Liver disease, American -Association forGastroenterology;The diagnosis and management of -non alcoholic fatty liver disease:practice guidelines -by the American Gastroenterological - Association, American -Association for thestudy of - Liver disease, American -Association forGastroenterology. Gastroenterology 2012;142:1592-609.

[80] Tziomalos K,Athyros VG,KaragiannisA. Nonalco-

DOI: https://doi.org/10.30564/jer.v3i2.3520

holic fatty liver disease in type2 Diabetes: pathogenesis -and treatment options. -Curr Vasc Pharmacol -2012;10:162-72.

[81] Kulvinder Kochar Kaur, Gautam Allahbadia, Mandeep Singh . 'Attempt to utilize Classification of Type2 Diabetes mellitus subgroups provided by Ahlqvist to generate individualized treatment methods based on the actions on insulin resistance & βcell function :A move forward to more effective diabetes control from start &avoid End StageDamage ''.2021 Under review.

[82] Dasarathy S, Dasarathy J,Khayami A,Yerian LM,Sergent R,McCollough AJ. Randomized controlled trial -of omega3 fatty acids -in the - treatment - of non alcoholic steatohepapititis -in type2 Diabetes mellitus. Hepatology 2013; 58:518a.

[83] Alam F,Islam MA,Mohammed M,Ahmad I,Kamal MA,Donelly R, et al. Efficacy and safety of Pioglitazone monotherapy in type2 Diabetes mellitus.:a systematic review and -meta-analysis of Randomized controlled trials.Sci Rep -2019;9:5389.

[84] Lebovitz HE. Thiazolidenediones :The forgotten Diabetic medications .Curr -Diab Rep 2019;19:151.

[85] Schernather G,Currie CJ, Schernather GH.Do we still need Pioglitazone for the treatment - of type2 Diabetes mellitus?a risk benefit critique in 2013. Diabetes Care 2013; 36:S155-S161.

[86] Vieira R,Souto SB,Sanchez-Lopez E,Machado AL,Severino P,Jose S, et al. Sugar lowering drugs for -type2 Diabetes mellitus and Metabolic Syndrome-review of classical and newcompounds. Pt1-Pharmaceuticals -2019;12:152.

[87] Tyagi SM,Gupta P,Sai niAS,Kaushal C,Sharma S.The Peroxisome Proliferator adenineActivated Receptor:a family of nuclear -Receptors --role in various diseases.J Adv Pharm Technol Res 2011;2:236-40.

[88] Choi SS,Park J, Choi JH.Revisiting PPAR -γ -as a target -for the treatment of Metabolic disorders .BMB Rep - -2014;47:599-608.

[89] Fonseca V.Effect of thiazolidenediones on body -weight -in patients type2 Diabetes mellitus.Am J Med -2003;115:42S-48S.

[90] Kang JG,Park CY.The actions of -PPAR -γ -agonists on the various -target organs .Korean J Obes -2011;20:161-69.

[91] Kawai T,Funae O,Shimada A,Tabata -M,Hirata T,Atsumi Y, et al. Effects of pre treatment with low dose metformin on metabolic - parameters and -weight gain by -Pioglitazonein Japanese -patients -with type2 Diabetes.Int -Med -2008;47:1181-188.

[92] Musso G,Cassander M,Paschetta E,Gambino R. Thiazolidenediones and advanced liverfibrosis -in non alcoholic steatohepatitis -:a meta-analysis.JAMA Int -Med -2017;177:633-40.

[93] Bril F,Kalavalapalli S,Clark VC,Lomonaco R,Soldevila-Pico C,Liu IC, et al.Response to Pioglitazonein - patients -with -non alcoholic steatohepatitis - with vs without type2 Diabetes. Clin Gastroenterol Hepatol -2018;16:558-66.

[94] Yuan G,Zhang ML,Gong ZJ.Effects of PPAR –g agonist Pioglitazoneon rat -hepatic fibrosis. World JGastroenterol2004;10:1047-51.

[95] Shah RA,Kowdley KV. Obeticholic acid for the treatment of non alcoholic steatohepapititis.Expert Rev Gastroenterol Hepatol -2020;14:311-21.

[96] Verbeke L,Mannaerts I,Shierwagen R,Govaore O,Klein S,Vander Elst I, et al.FXR against Obeticholic acid reduces -hepatic inflammation and fibrosis in a rat model of toxic cirrhosis. Sci Rep -2016;6:33453.

[97] Li T,Francl JM,Boehme S,Chang JY. Regulation of cholesterol and Bile acid homeostasis by the cholesterol7α hydroxylase / steroid -response -element binding protein 2/micro RNA-33a in mice. Hepatology 2013; 58:1111-121.

[98] Pelliciari R, Costantino G, Camaioni E,Sadeghpour BM,Entrena A,Willson TM, etal . Bile acid derivatives -as ligands of the -Farsenoid X receptor:synthesis, evaluation and structure Activity relationship -of a series of body and side chain modified analogues -of -chenodeoxycholic acid. J Med Chem - -2004; 47:4559-69.

[99] Mudaliar S,Henry RR,SanyalAJ,Morrow L,Marshall HU,Kipnes M, etal .Efficacy and safety of the -Farsenoid X receptor agonist Obeticholic acid in patients -withtype2 Diabetes mellitus and -of -non alcoholic fatty liver disease. Gastroenterology -2013; 145:574-82.

[100] Hameed B, Terrault NA,Gill RM,Loomba R, Chalasani N,Hoofnage JH, etal .The NASH Clinical research network. Clinical and metabolic effects associated -with -weight changes -and - Obeticholic acid in non alcoholic steatohepatitis. Aliment -Pharmacol -Ther 2018;47: 645-56.

[101] Hindson J. Obeticholic acid for the treatment of non alcoholic steatohepapititis. Nat Rev Gastroenterol Hepatol 2020; 17:65.

[102] Berger J,Moller DE.The mechanisms of action of PPARs. Annu Rev Med -2002;53: 409-35.

[103] Connolly JJ,Ooka K,Lim JK,Future Pharmacotherapy -for non alcoholic steatohepapititis(NASH):review in phase 2 and 3 trials.J Clin Transl Hepatol

 DOI: https://doi.org/10.30564/jer.v3i2.3520

2018; 6:264-75.

[104] Pawlak M,Lefebvre P,Staels B. Molecular mechanisms of PPARα action and its impact on lipid metabolism , inflammation and fibrosis -in non alcoholic steatohepatitis. -J Hepatol 2015;62: 720-33.

[105] Musso G,Gambino R,Cassader M,Pagano G.A meta-analysis for the randomized -trials -for the treatment of non alcoholic -Fatty Acid Liver Disease. Hepatology 2010; 52:79-104.

[106] Bojic LA,Huff MW. Peroxisome Proliferator Activated Receptorδ:A multifaceted -metabolic player. Curr Opin Lipiodol 2013;24: 171-7.

[107] Karpe F,Ehrenborg EE.PPARδ in humans:genetic -and Pharmacologic evidence for a significant Metabolic -function. Curr Opin Lipiodol 2009;20: 333-6.

[108] Riserus U,Sprecher D,Johnson T,Olson E,Hirschberg S,Liu A, etal. Activation of Peroxisome Proliferator Activated Receptorδ(PPAR -δ)promotes reversal of multiple metabolic abnormalities ,reduces Oxidative stress,and increases fatty acid oxidation in moderately obese men. Diabetes 2008;57: 332-9.

[109] Ratziu V,Harrison SA,Francque S,Bedossa P,Lahert P,Serfaty L, etal .GOLDEN 505 Investigator Study Group. Elafibranor,an agonist of -the Peroxisome Proliferator Activated Receptor α,and δ induces resolution of non alcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016; 150:1147-59.

[110] Briand F,Heymes C,Bonada L,Angles T,Charpentier J,Branchereau M, etal.A 3week non alcoholic steatohepapititis mouse model -shows Elafibranor benefits -on hepatic inflammation and cell death. Clin Transl Sci 2020; 13:529-38.

[111] Tolbol KS,Kristiansen MN,Hansen HH,Veidal SS,Rigbolt KT, etal. Metabolic and hepatic effects of Liraglutide, Obeticholic acid and Elafibranor in diet induced obese -mouse model of biopsy confirmed non alcoholic steatohepatitis. -World JGastroenterol2018;24:179-94.

[112] Briand F,Maupoint J, BrousseauE,Breyner N,Bouchet M,Costard C, etal. Elafibranor improves diet induced non alcoholic steatohepatitis associated -with heart failure with preserved ejection fraction -in golden Syrian hamsters. Metabolism 2021; 117:154707.

[113] Cariou B,Hanf R,Lambert –Porcheron S,Zair Y,Sauvinet V, etal.Dual Peroxisome Proliferator Activated Receptor α,and δ agonist GFT505 improves hepatic and peripheral insulin sensitivity in abdominally obese -subjects. Diabetes Care 2013; 36:2923-930.

[114] Cariou B, Zair Y,Staels B,Bruckert E. Effects of -the new dual PPARα / δ agonist GFT505 on lipid and glucosehomeostasis in abdominally obese -patients with combined dyslipidemia or impaired glucose metabolism. Diabetes Care 2011; 34:2008-14.

[115] Jeong SW. Non alcoholic fatty liver disease:A Drug revolution is coming. Diabetes Metab J 2020;44:640-57.

[116] Irruarrizaga-Lejarreta M,Varela –Rey M, Fernandez-RamosD, Martinez-A rranz I,Delgado TC, etal. Role of Aramchol in steatohepapititis and - -fibrosis in mice . Hepatol Commun2017;1: 911-27.

[117] Dobrzyn A,Ntambi JM. Stearoyl-Co A Desaturase as a new drug for obesity treatment. ObesRev 2005;6:169-74.

[118] Goldiner I,Van der Velde AE,Vandenberghe KE,Van wijland MA,Halpern Z,Gilat T, etal.ABCA1 – dependent but apoA1 independent - cholesterol efflux -mediated by fatty acids -bile acid conjugates(-FABACs).Biochem J 2006;396:529-36.

[119] Safaldi K,Konikoff FM,Mahmaid M,Zelber –Sagi S,Halpern N,Gilat T etal.The fatty acids -bile acid conjugate Aramchol reduces liver fat content in Non Alcoholic Fatty Acid Liver Disease. Clin Gastroenterol Hepatol 2014; 12:2085-91.

[120] Gentiella R,Pechtner V,Corcos A,Consoli A. Glucagon like peptide 1 receptor -agonists in type2 -Diabetes treatment :are they all the same? Diabetes -Metab Res Rev 2019; 35:e3070.

[121] Greiner TU,Backhed F.Microbial regulation of GLP-1 and L-cell biology . -Mol Metab 2016;15:753-58.

[122] Michalowska J,Miller-Kasprzak E,Bogdanski P. Incretin -hormones in obesity -and related cardiometabolic disorders;the Clinical perspective. Nutrients -2021;13:351.

[123] Armstrong MJ,Gaunt P,Aithal GP,Barton D,Hull D,Parker R, etal .LEAN trial team .Liraglutidesafety and efficacy in for patients with non alcoholic steatohepatitis(LEAN):a multicenter ,double blinded , a -randomized,placebo- controlled -phase 2 -study . Lancet 2016; 387:679--90.

[124] DeFronzo RA,Ratner R,Han J,Kim D,Fineman M etal. Effects of Exenatide (Extendin-4)on glycemic control and weight control over 30weeks in metformin treated patients with type2 - Diabetes. Diabetes Care 2005; 28:1092-100.

[125] Crane J,McGowan B.The GLP-1 agonists, Liraglutide,as a pharmacotherapy for obesity.Ther Adv Chronic Dis - 2016; 7:92-107.

DOI: https://doi.org/10.30564/jer.v3i2.3520

[126] Davies MJ,Aronne LJ,Caterson ID,Thomsen AB,Jacobsen PB,Marso SP. Liraglutide and cardiovascular outcomes -in adults for obesity:a posthoc analysis from the SCALE -Diabetes randomized controlled trials. Diabetes Obes Metab 2018;20:734-39.

[127] AdamsJM,Pei H,Sandoval DA,SeelyRJ,Chang RB,-Liberles SD, etal. Liraglutide modulates appetite and body weight through Glucagon like peptide 1 receptor -expressing glutamatergic neurons. Diabetes -2018;67:1538-48.

[128] Mantovani A,Petracca G,Beatrice G,Csermely A,Lonardo A,Targher G. Glucagon like peptide 1 receptor -agonists for treatment of Non Alcoholic Fatty Acid Liver Disease and Non Alcoholic steatohepapititis:an updated meta-analysis of randomized controlled trials. Metabolites -2021;11:73.

[129] Kapodistria K,Tsilibary EP,KotsopouloE,Moustardas P,Kitsiou P. Liraglutide,A human Glucagon like peptide 1 analogue ,stimulates AKT dependent -survival signaling.J Cell Mol Med 2018;22:2970-980.

[130] HeQ,Sha S,Sun L,Zhang J,Dong M. GLP-1 analogueimproves - hepatic lipidaccumulation by inducing -autophagy via AMPK/ mTOR pathway. Biochem -Biophys Res Commun -2016;476:196-203.

[131] Chalasani N, Younossi ZM, Lavine AE, Diehl AM,Brunt EM,Cusi K,Sanyal AJ. The diagnosis and management of -non alcoholic fatty liver disease:practice guidelines -by the American Gastroenterological - Association, American -Association for thestudy of - Liver disease, American -Association forGastroenterology. Hepatology 2012;302:G225-G235.

[132] Nelson CH,Etchevers K,Yi S,Breckenridge D,Hepner M,Patel U etal.Pharmacokinetic ,safety and tolerability of Selonsertib,an apoptosis signal regulating kinase 1(ASK1) Inhibitor), following first -in human single and multiple ascending doses in healthy subjects.Clin Pharmacokinet 2020;59:1109-17.

[133] Budas G,Karnic S,Johnson T,Shafideh T,Watkins S , Breckenridge D, etal. Reduction of Liver steatosis and fibrosis -with an ASK1 Inhibitor in murine model of NASH is accompanied by improvements in cholesterol, the bile acid and lipid metabolism.J Hepatol -2016;64:S170.

[134] Loomba R, Lawitz EJ,Mantry PS, Jayakumar A, Caldwell SH,Arnold H etal.The - ASK1 Inhibitor Selonsertib in - patients with Non Alcoholic steatohepapititis:a randomized phase 2 - trial. Hepatology 2018;67:549-59.

[135] Dickson I.No antifibrotic effects of Selonsertib in NASH. Nat Rev Gastroenterol Hepatol 2020; 17:260.

[136] Puente A,Fortea JL,Cabezas J,Arias Loste MT,Iruzubieta P,Llerena S, etal.LOXL2;A new target in antifibrogenic therapy. Int J MolSci 2019;20:1634.

[137] Rodriguez HM,Vaysberg M,Mikels A,McCauley S,Velayo AC,Garcia C, etal.Modulation of lysyl oxidase –like 2 enzymatic activity by an allosteric antibody Inhibitor.J Biol Chem 2010;285:20964-20974.

[138] Lipson KE,Wong C,Teng Y,Spong S.CTGF is a central mediator of tissue remodeling and its inhibition can reverse the fibrosis.Fibrogenesis T issue Repair 2012;5:S 24.

[139] Harrison SA, Abdelmalek MF, Caldwell SH,Shiffman ML, Diehl AM,Ghalib R etal.Simutuzumab -is ineffective for patients with bridging fibrosis or compensated cirrhosis caused by) -non alcoholic steatohepapititis. Gastroenterology 2018;155:1140-53.

[140] Marra F, Tacke F.Roles of chemokines - in liver disease. Gastroenterology 2014;147:577-94.

[141] Kim BM,Abdelfattah AM,Vasan R,Fuchs BC,Choi MY. Hepatic Stellate cells -secrete Cc15 to induce hepatic steatosis.Sci Rep 2018;8:7499.

[142] Friedman SL, Sanyal AJ, Goodman SM, Lefebvre E,Gottwald M,Fischer L, Ratziu V.Efficacy and safety -study of cenicriviroc for treatment of -non alcoholic steatohepatitis in adult subjects with Liver fibrosis:CENTAUR Phase 2b study design.Contemp Clin Trials2016; 47:356-65.

[143] Friedman SL, Ratziu V,Harrison SA, Abdelmalek MF, Aithal GP,Caballeria J, etal .A randomized,placebo- controlledtrial of cenicriviroc for the treatment of -non alcoholic steatohepatitis with fibrosis. Hepatology 2018; 67:1754-67.

[144] Anstee QM,Neuschwander –Tetri BA,Wong VW, Abdelmalek MF, Younossi ZM,Yuan J, etal. - Cenicriviroc for the treatment of -liver fibrosis in adults with - of -non alcoholic steatohepatitis:AURORA phase 3 -study design. Contemp Clin Trials2020; 89:105922.

[145] Boutari C,Perakakis N,Mantzoros CS. Association of Adipokines with development of , non alcoholic fatty liver disease.Endocrinol Metab 2018;33:33-43.

[146] Polyzos SA,Kountouras J, Mantzoros CS.Leptin in non alcoholic steatohepatitis:a narrative review. Metabolism -2015;64:60-78.

 DOI: https://doi.org/10.30564/jer.v3i2.3520

[147] Jamali R,Arj A,Razavizade M,Aarabi MH.Prediction of non alcoholic fatty liver disease via a novel panel of serum Adipokines.Medicine -2016;95:e2630.

[148] Polyzos SA,Kountouras J,Anastasilakis AD,Geldari EV, Mantzoros CS. Irisin in -patients -with -non alcoholic fatty liver disease . Metabolism -2014;63:207-17.

[149] Zhang SR,Fan ZM. Ghrelin- ghrelin-O-Acetyl transferase system -in the pathogenesis of non alcoholic fatty liver disease. World J Gastroenterol2015;21:3214-22.

[150] Arvaniti VA,Thomopoulos KC,Tsamandas A,Makri M,Psyrorogiannis A,Vafiadis G, etal .Serum adiponectin -levels in different types of non alcoholic fatty liver disease: correlation with - -steatosis,necro inflammation and -fibrosis.Acta Gastroenterol Belg -2008;71:355-60.

[151] Garinis GA,Fruci B,Mazaa A,DeSienna M,Abenavoli A,Gulletta E, etal.Metformin -versus dietary -treatment of -non alcoholic steatohepatitis.Int J Obes -2010;34:1255-64.

[152] Ryan MJ,Dudash HJ,Docherty M,Geronilla KB,-Baker BA,Haff GG, etal. Vitamin E and Csupplementation -reduces Oxidative stress improves antioxidant tenzymes -and positive muscle work -in chronically loaded muscles -of aged rats .Exp Gerontol -2010;45:882-95.

[153] Balmer ML,Siegrist K,Zimmermann A,Dufour JF.Effect of ursodeoxycholic acid in combination with Vitamin E on Adipokines and apoptosis in patients with non alcoholic steatohepatitis. Liver Int -2009; 29:1184-88.

[154] Otabe S,Yuan X,Fukutani T,Wada N,Hashinaga T,Nakayama H, etal.Over expression of human -adiponectin -in transgenic mice - results in suppre ssion of fat accumulation and prevention of premature death -by high calorie diet. Am J Physiol Endocrinol Metab -2007;293:E210-E218.

[155] Sharma D,Wang J,Fu PP, Sharma S,Nagalingam A,Mells A, etal. Adiponectin antagonizes the oncogenic actions of leptin in Hepatocellular carcinogenesis. Hepatology 2010; 52:1713-22.

[156] Kelesidis T, Kelesidis I,Chou Z, Mantzoros CS.Narrative review:The role of leptin in human -physiology:emerging Clinical applications .Ann Intern Med 2010;152:93-100.

[157] Unger RH.Lipotoxic diseases, Annu -Rev Med 2002;53:319-36.

[158] Ikejima K,Honda H,Yoshikawa M,Hirose M,Kitamura T,Takei Y, etal.Leptinaugments inflammatoryand profibrogenic -responses in the murine liver induced by hepatoxic chemicals. Hepatology 2001; 34:288-97.

[159] Polyzos SA,Aronis KN,Kountouras J,Raptis DD,Vasiloglu MF, Mantzoros CS. Circulating leptin in non alcoholic fatty liver disease:a systematic review and -meta-analysis. Diabetologia --2016;59:30-43.

[160] Muse ED,Obici S,Bhanot S,Monia BP,McKay RA,Rajala MW, etal.Role of resistin -in diet induced hepatic insulin resistance.J Clin Invest -2004; 114:232-39.

[161] Bertolani C,Sancho Bru P,Failli P,Batallier R,Aleffi S,DeFranco R, etal. Resistin as an intra hepatic cytokine : Over expression during chronic injury and induction of proinflammatory action in -hepatic stellate -cells.Am J Pathol -2006; 169:2042-53.

[162] Jamali R, Razavizade M, Arj A,Aarabi MH. Serum adipokines might predict liver histology findings -in - non alcoholic fatty liver disease. World J Gastroenterol2016;22:5096-103.

[163] Rasouli N,Yao-BorengaaserA,Miles LM,Elbein SC,Kern PA.Increased plasma Adiponectin in response to Pioglitazone does not result from Increased gene expression . Am J Physiol Endocrinol Metab -2006;290:E42-E46.

[164] Delporte C. Structure -and physiological actions of -ghrelin.Scientifica 2013; 2013:518909.

[165] Purnell JQ,Weigle DS,Breen P,Cummings DE. Ghrelin levels correlate with insulinlevels, insulin resistance,and high density lipoprotein cholesterol ,but not with gender ,menopausal status -or cortisol -levels in humans. J Clin Endocrinol Metab -2003;88:5674-79.

[166] LiY,Hai J, Li L,Chen X,Peng H,Cao M, etal. Administration -of Ghrelin improves inflammation, Oxidative stress,and apoptosis during -and after non alcoholic fatty liver disease development.Endocrine 2013;43:376-86.

[167] Mao Y,Cheng J,YuF,LiH,GuoC,Fan X. Ghrelin attenuated lipotoxicity via autophagy induction .Cell Physiol Biochem -2015;37:563-76.

[168] Schnyder S,Handschin C. Skeletal muscle as an endocrine organ:PGC-1α,myokines and exercise.Bone -2015;80:115-25.

[169] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Therapeutic Applications of the Recent Understanding of Brown or "Beige" Adipocyte Physiology. Adv Tech Biol Med -2015; 3: 128.
DOI: 10.4172/2379-1764.1000128.

[170] Zhang Y,Li R,Meng Y,LiS,Donelan W,Zhao Y,

DOI: https://doi.org/10.30564/jer.v3i2.3520

etal. Irisin stimulates browning of white adipocytes through -mitogen activated protein kinase p38MAP Kinase and ERKMAP Kinase Signaling. Diabetes -2014;63:514-25.

[171] Polyzos SA,Mathew H, Mantzoros CS. Irisin:A true, circulating hormone. Metabolism 2015;64:1611-18.

[172] Perez –Soleto D,Roca –RivadaA,BaamondeI,Baltar J,Castro AI,Dominguez E, etal.Lack of adipocytes-Fndc5/ Irisin expression -and secretion reduces thermogenesis and enhancesadipogenesis.Sci Rep -2017;7:16289.

[173] Muir AJ,Levy C,Janssen HLA,Montano-Loza AJ,-Shiffman ML, Caldwell S, etal. Simutuzumab for primary - sclerosing -cholangitis: phase 2 study results with insights -on the natural history of -disease. Hepatology 2019; 69:684-98.

[174] Chen P,Chung FM,Chang DM,Tsai JC,Huang HF,Shin SJ, etal.Elevated plasma levels of visfatin/ preB cell colony-enhancing factor in treated patients with type2 - Diabetes. -J Clin Endocrinol Metab -2006;91:295-9.

[175] Mousavi Z,Ganji A,Farrokh Tehrani D,Bahari A,Esmeil Zadeh A,Delghadi M. Correlation of visfatin-levels with non alcoholic fatty liver in Metabolic Syndrome.J Islam Republic Iran 2017;31:28.

[176] KadoglouNP, Tsanikidis H,Kapelozou A,Vrabas I,Vitta I,Krayannacos PE, etal.Effect of -ofrosiglitazone -and metformin treatment - on apelin, visfatin ghrelin levels in -patients with type2 - Diabetes .Metabolism 2010;59:373-79.

[177] Kim E,Voatour P. Hepatocellular carcinoma:Old friends and new tricks.Exp Mol Med2020; 52:1898-1907.

[178] CholankerilG,Patel R,,Khurana S,Satapathy SK. Hepatocellular carcinoma in non alcoholic steatohepatitis:current -knowledge and implications for management. World JHepatol 2017; 9:-533-43.

[179] Jing YY,Han Z,Sun K,Zhang SS,Hou J,Liu Y, etal. Toll like receptor 4 signaling promotes epithelial –mesenchymal transition in human - Hepatocellular carcinoma induced by lipopolysaccharides.BMC Med 2012;10:98.

[180] Li H, Li Y, LiuD, LiuJ.LPS promotes epithelial –mesenchymal transition and activation of -TLR4/ JNK signaling.Tumor -Biol -2014;35:10429-35.

[181] Gupta H,Youn GS,Shin MJ,Suk KT. Gut microbiota in Hepatocarcinogenesis. Microorganisms -2019;7:121.

[182] Saxena NK,FuPP,Nagalingam A, Wang J,Handy J,Cohen C, etal. Adiponectin modulates -c –jun N terminal kinase -and mammalian target of rapamycin -and inhibits Hepatocellular carcinoma. Gastroenterology -2010;139:1762-73.

[183] Al-Gayyar AM,Abbas A,Hamdan AM.Chemopreventive -and hepatoprotective -role of Adiponectin(SULF2 Inhibitor) in Hepatocellular carcinoma. Biol Chem 2016;397:257-67.

[184] Kamada Y,Matsumoto H,Tamura S,Fukushima J,Kiso S,Fukui K, etal.Hypo Adiponectinemia accelerates hepatic tumorformation - -in non alcoholic steatohepatitis mouse model.J -HepatoL -2007;47:556-64.

[185] Shen J,Yeh CC,Wang Q,Gurvich I,Siegel AB, etal. Plasma Adiponectin and Hepatocellular carcinoma survival -among patients without liver transplantation.Anticancer Res 2016;36:5307-14.

[186] Wei R,Hu Y,Dong F,Xu X,Hu A,Gao G. Hepatoma -cell-derived leptin down regulates -the immunosuppressive function of regulatory T cells -to enhance the anti tumor activity of CD 8+T cells -.Immunol Cell Biol -2016;94:388-99.

[187] Stefanou N,Papanilkolaou V,Furukawa Y,Nakamura Y,Tsezou A. Leptin as acritical regulator of Hepatocellular carcinoma development through modulation of human telomerase -reverse transcriptase. BMC Cancer -2010;10:442.

[188] Levielle M,Estall JL. Mitochondrial dysfunctionin the transition - from -NASHto HCC. Metabolites -2019;9:233.

[189] Nakagawa H,Umemura A,Taniguchi K,Font –Burgada J,Dhar D,Ogata H, etal.ER Stress -cooperates with hypernutrition to trigger TNF dependent -spontaneous HCC development. Cancer Cell -2014;26:331-43.

[190] Von Loeffelholz H,Horn P,Birkenfeld AL,Claus RA,Metzing BU,Docke S, etal.Predictor of liver fat -in preoperative patients with non alcoholic fatty liver disease. J Invest Surg -2016;29:266-74.

[191] Peter A,Kovarova M,Staiger H,Mechann J,Schick F,Konigsrainer A, etal.The Hepatokines Fetuin A and -Fetuin B -are upregulated in the state of hepatic steatosis and may differently impact -on glucose-homeostasis in humans. Am J Physiol Endocrinol Metab -2018;314:E266-E273.

[192] Cui Z,Xuan R,Yang Y.Serum Fetuin A level is associated -with non alcoholic fatty liver disease in Chinese population.Oncotarget -2017; 8:-107149-107156.

[193] Mukhuty A,Fouzder C,Mukherjee S,Malick C,Mukhopadhyay S,Ray S, etal. Fetuin A secretion from Pancreatic βcells - -adversely affects -its function and elicits inflammation. Biochem -Biophys Res

 DOI: https://doi.org/10.30564/jer.v3i2.3520

Commun -2017;491:1118-24.

[194] -Dasgupta S,Bhattacharya S,Biswas A,Majumdar SS, Mukhopadhyay S,Ray S, etal. -Nuclear factor kappa Bmediates -lipid-induced Fetuin A expression in hepatocytes -that improve adipocyte -function effecting insulin resistance.Biochem J -2010;429:451-62.

[195] Mori K,Emoto M, Araki T,Yokoyama H,LeeH ,Taramura M, etal. -Effects of Pioglitazone on Serum Fetuin A levels -in -patients with type2 - Diabetes. Metabolism 2008;57:1248-52.

[196] Ochi A, Mori K,Emoto M, Nakatani N, Morioka T,Motoyama K, -etal.Direct inhibitory -Effects of Pioglitazone on -hepatic -Fetuin A expression.PLoS One -2014;9:e88704.

[197] Li L,Gu X,Fang M,JiJ,YiC,Gao C.The diagnostic value of Serum fucosylated Fetuin A in hepatitis Bvirus related liver diseases. Clin - Chem LabMed -2016;54:693-701.

[198] Pan X,Kaminga AC,Chen J,Luo M, LuoJ. Fetuin A and -Fetuin B - in non alcoholic fatty liver disease:a meta-analysis and -meta regression. Int JEnviron Res -Public Health2020;17:2735.

[199] Meex RC,Hoy AJ,Morris A,Brown RD,LoJC,Burke M, etal. -Fetuin B -is a -secreted hepatocyte factor -linking steatosis to impaired glucose metabolism. Cell Metab 2015;22:1078-89.

[200] Zhou W, Yang -J,Zhu J, Wang -Y,Wu Y,Xu L, etal. -Fetuin B - aggravates -liver X receptor mediated -hepatic steatosis -through AMPK in Hep G2 cells in mice .Am J Transl Res -2019;11:1498-1509.

[201] Ebert T,Linder N,Schaudinn - A,Busse H,Berger J,Lichtinghagen R, etal. -Association of -Fetuin B - with markers of liver fibrosis in non alcoholic fatty liver disease .Endocrine 2017;58:246-52.

[202] Zhong G,Kirkwood J,Won KJ,Tjota N,Jeong H,Isoherranen N. Characterization of Vitamin A metabolome -in human livers with and -without non alcoholic fatty liver disease.J Pharmacol -Exp Ther 2019;370: 92-103.

[203] Perduca M,Nicolis S.Mannuci B,Galliano M,Monaco HL.Human plasma Retinol Binding protein -4(RBP4) is also a fatty acid Binding protein. Biochim -Biophys Acta Mol Cell Biol Lipids 2018;1863:458 -66.

[204] Wang X,Chen X, Zhang H,Pang J,Lin J, Xu X, etal. Circulating -Retinol Binding protein 4is associated -with development -and regression of non alcoholic fatty liver disease. Diabetes Metab 2020;46: 119-28.

[205] Graham TE, Yang Q,Bluher M,Hammarstedt A,Ciaraldi TP,Henry RR, etal. Retinol Binding protein 4 and insulin resistance in lean ,obese and diabetic -subjects. NEngl J -Med 2006;354:2552-63.

[206] Petta S,Tripodo C,Grimaudo S,Cabibi D,Camma C,DiCristina A, etal.High liver RBP4 protein content -is -associated -with histological features in patients with genotype1 chronic hepatitis C and with non alcoholic steatohepatitis. Dig -Liver Dis -2011;43:404-10.

[207] Bahr MJ,Boeker KH,Manns MP,Tietge UJ.Decreased hepatic - RBP4 -secretion -is correlated with - -reduced levels -hepatic - glucose -production but is not -associated -with insulin resistance in patients with cirrhosis.Clin -Endocrinol -2009;70:60-5.

[208] Hara H,Uchida S,Yoshi mura H.Aoki M,Toyoda Y,Sakai K, etal.Isolation and -Characterization ofa novel liver specific gene, Hepassocin,upregulated -during liver regeneration. Biochim -Biophys Acta -2000;1492:31-44.

[209] Abdelmeomen G,Khodeir S,Zaki AN,Kasaab M,Abou Saif S,Abd Elasam S.Over expressionof -Hepassocin in diabetic -patients with non alcoholic fatty liver disease may facilitate increased -hepatic lipid accumulation. Endocrin Metab Immune Disord Drug Targets - 2019;19: 185-8.

[210] Wu HT,Lu FH,OuHY,Su YC,Hung HC, Wu JS, etal. The role of Hepassocin in the development of non alcoholic fatty liver disease. -J Hepatol 2013;59: 1065-72.

[211] Cheng KP, OuHY, Hung HC,LiCH,Fan KC, Wu JS, etal. Unsaturated fatty acids increase the expression of Hepassocin through a Signal -Transducers and Activators of Transcription3 dependent pathway in HepG2 cells.Lipids - 2018;53:863-69.

[212] Jung TW, Chung YH,Kim HC, Abd -El-Aty AM, Jeong JH.Hyper lipidemia-induced -Hepassocin in the liver contributes -to insulin resistance in skeletal muscle. - MolCell Endocrinol2018; 470:26-33.

[213] YuHT, Yu M,Li CY,Zhan YQ,Xu WX, Li -YH , etal. Specific - expression of -and regulation -of Hepassocin - in the liver and down regulation -of the correlation of -HNF1 alpha with decreased levels of Hepassocin in human Hepatocellular carcinoma. J Biol Chem 2009;284:133335-1313347.

[214] Li CY,Cao CZ, Xu WX, Cao MM, Yang F,Dong L, etal. Recombinant human -Hepassocin -stimulates -proliferation of hepatocytes -in vivo and improves survival -in -Hepatocellular carcinoma.Gut -2010;59:817-26.

[215] Yan J, Yu Y, Wang N, Chang Y,Ying H, Liu W, etal.

DOI: https://doi.org/10.30564/jer.v3i2.3520

LFIRE1/HFREP-1,a liver Specific - gene is frequently -down regulated and has growth suppressor activity in Hepatocellular carcinoma. Oncogene -2004;230:1939-49.

[216] Pan J,Parlee SD,Brunel FM, Li P,LuW,Perez-Tilve D, etal.Optimization of peptide inhibitors of β-Klotho as antagonists of Fibroblast -growth -factor 19 and -21.ACS Pharmacol Transl Sci -2020;3:976-86.

[217] Wu AL,Coulter S,Liddle C,Wong A,Eastham-Anderson J,French DM, etal.FGF19 regulates cell proliferation, glucose and bile acid metabolism via FGFR4 -dependent and independent pathways. PLoS One -2011;6:e17868.

[218] Jiao N,Baker SS,Chapa-Rodriques A, Liu W,Nugent CA,Tsompana M, etal.Suppressed hepatic bile acid signaling despite elevated production of primary -and secondary bile acids in NAFLD.Gut -2018;67:1881-91.

[219] Li Y,Zhang W,Doughtie A,Cui G, Li X,Pandit H, etal.Upregulation of Fibroblast -growth -factor 19 and its receptor associates -with -progression from -fatty liver to Hepatocellular carcinoma. Oncotarget -2016; 7:-52329-52339.

[220] Chen L, Liu H, Liu J,Zhu Y,Xu L,HeH, etal.Klotho endows hepatoma cells -with resistance to anoikis -via VEGFR 2/PAK1 activation in -Hepatocellular carcinoma. PLoS ONE -2013;8:e58413.

[221] Gong Q,HuZ, Zhang F,Cui A, Chen X,Jiang H, etal. Fibroblast -growth -factor 21 improves insulin sensitivity by inhibiting mammalian target of rapamycin complex1 in mice . Hepatology 2017; 64:425-38.

[222] Hong ES,Lim C,Choi HY,Lee YK.KuEJ,Moon JH, etal.Plasma of Fibroblast -growth -factor 21 levels increase with ectopic fat accumulation -and its receptor levels -are decreased in the visceral fat of in -patients with type2 - Diabetes .BMJ Open Diabetes Res Care 2019;7:e00076.

[223] Flisiak-IackiewiczM, Bobrus-Chociej A, Wasilewska M, Tarasow E,WojtowskaM, Lebenszejn DM. Can Hepatokines be regarded as novel noninvasive serum biomarkers -of intraHepatic liver -content in obese -children?Adv Med Sci -2019;64:30484.

[224] Rusli F,Deelen J,Andriyani E,Boekschoten MV,Lute C,Van den Akker EB, etal. Fibroblast -growth -factor 21 reflects liver fat accumulation - and dysregulation of signaling pathways in the liver -of C57BL/6J mice.Sci Rep - 2016; 6:30484.

[225] Yang M,Xu D, Liu Y,Guo X, Li W, Guo C, etal. Combined serum -biomarkers in noninvasive -diagnosis of non alcoholic steatohepapititis. PLoS ONE -2015;10:e131664.

[226] Yang C, Lu W,Lin T,You P,YeM,Huang Y, etal. Activation - of liver FGF21 -in Hepatocarcinogenesis and during Hepatic stress .BMC -Gastroenterol 2013; 13:67.

[227] Kong FJ,MaLL,LiG,Chen YX,Zhou JQ,Circulating betatrophin levels an d gestational Diabetes mellitus:a systematic review and -meta-analysis -. PLoS ONE -2017;12:e016994.

[228] Lee YH, Lee SG, Lee CJ,Kim SH,Song YM,Yoon MR, etal. Association between betatrophin/ ANGPTL8 and non alcoholic fatty liver disease:animal and human studies. Sci Rep - 2016; 6:24013.

[229] Zhang R.The -ANGPTL3-4-8 model ,a molecular -mechanism for triglyceride trafficking .Open Biol -2016; 6:150272.

[230] Yin Y,Ding X,Peng L,Hou Y,Ling Y,GuM, etal.Increased serum ANGPTL8 concentrations in patients -with pre Diabetes and -type2 - Diabetes.J Diabetes Res 2017; 2017:8293207.

[231] Gusarova V,Alexa CA,Na E,Stevis BE,Xin Y,-Bonner-Weir S, etal. ANGPTL8/ betatrophin does notcontrol Pancreatic βcells - expansion.Cell -2014; 159:691-6.

[232] Zhang L,Shannon CE, TM,Abdul –Ghani MA,-Fourcaudot M,Norton L.Regulation of ANGPTL8 in liver -and adipose tissue by nutritional and hormonal signals and the effect on glucosehomeostasis in mice. Am J Physiol Endocrinol Metab -2020;318:E613-E624.

[233] Chen YQ,Pottanat TG,Siegel RW,Ehsani M,Qian YQ,Zhen EY, etal. Angiopoietin –Like Protein- 8 differentially regulates ANGPTL 3 and ANGPTL 4 during postprandial -partitioning of fatty acids.J Lipid Res - 2020;61:1203-20.

[234] Dijk W,Kersten S.Regulation of -Lipid metabolism by Angiopoietin –Like Protein's . Curr Opin Lipiodol 2016;27: 249-56.

[235] Yoshida K,Shimizugawa T,Ono M,Furukawa H. Angiopoietin –Like Protein 4 is a potent hyperlipidemia-inducing factor in mice and inhibitor of lipoprotein lipase. J Lipid Res - 2002;43:1770-72.

[236] Ng KT,Xu A,Cheng Q,Guo DY,Lim ZX,Sun CK, etal. Clinical relevanc e -and therapeutic potential -of -Angiopoietin –Like Protein 4 in Hepatocellular carcinoma.Mol Cancer 2014;13:96.

 DOI: https://doi.org/10.30564/jer.v3i2.3520

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ARTICLE

Post-surgery Quality of Life in Patients with Acromegaly Using SF36 Quality of Life Questionnaire-prospective Study

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ABSTRACT

Introduction: Acromegaly is chronic progressive disease with multisystem involvement characterised by an excess secretion of growth hormone and increased circulating insulin like growth factor 1 concentration.
Aims and Objectives: To assess surgical outcome of acromegaly patients at tertiary care institute using SF 36 quality of life questionnaire. SF-36 scores comprise 3 components: the physical component summary (PCS), the mental component summary (MCS) and role-social component summary (RCS).
30 acromegaly patients admitted in Guwahati medical college were enrolled in study and followed up post operatively for surgical remission. All participants completed the SF-36 preoperatively, 1 year and 2 years postoperatively.
Material and Method: Out of 30 patients 6 patients had surgical remission post operatively on the basis of postoperative glucose suppressed GH Level done after 12 weeks. Preoperatively subscale scores (physical functioning, role physical, general health) which were below the set standards for the normal population show significant postoperative improvements along with mental health (MH) scores. Similarly, PCS, MCS and RCS scores changed significantly after surgery. We also compared the QOL of 6 patients whose peak GH level was < 0.4 μg/L during postoperative oral glucose tolerance testing with those patients whose nadir GH level was ≥ 0.4 μg/L. There was significant difference between partial and complete remission group in subscale score role physical, social function and mental health. Similarly, PCS and RCS score significantly different in partial and complete remission group than MCS score.
Conclusions: QOL is considerably reduced in patients with acromegaly compared to general population which improves significantly after surgical treatment. Patients achieving the new remission criteria had significant improvement in physical and social components than those who did not.

1. Introduction

Acromegaly is a chronic illness characterised by changes in appearance, skeletal deformities and various metabolic disorders. In 95% of cases, acromegaly is caused by excessive secretion of the growth hormone (GH) by a hormonally active adenoma of the anterior lobe of the pituitary gland (GHoma) which in turn leads to excessive secretion of insulin-like growth factor-1 (IGF-1). Excessive secretion of IGF-1 results in bone and soft tissue proliferation in the distal extremities, the jaw, tongue, lips, nose and the frontal eminence. Disease control by vari-

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ous means can improve metabolic function, improve life expectancy and reduce morbidity [1-3]. Metabolic abnormalities associated with acromegaly lead to cardiac hypertrophy, heart failure and increased incidence of ischemic heart disease which is the leading cause of death in patients with acromegaly [4-5]. The introduction advanced surgical techniques have significantly improved the cure rate of acromegaly patients [6-8]. Remission of acromegaly is usually defined on the basis of 3 month post-operative suppressed GH< 1 ug/l, however according to a new consensus guideline based on GH suppression to < 0.4 µg/L and age and sex adjusted IGF 1 level is recommended [9]. We do not know the effect of surgical remission on the post-operative QOL in patients with acromegaly and also of new consensus criteria. So, we conducted this study to assess the effect of surgical treatment on quality of life using SF36 questionnaire in a prospective cohort of acromegaly patients. We also evaluated the quality of life in patients who have achieved remission according to new consensus criteria.

2. Material Methods

30 newly diagnosed acromegaly patients (14 men and 16 women) based on clinical, biochemical and radiological features with an average age of 44.5 years (range 21-67) were included in study. The diagnosis of acromegaly was confirmed with post oral glucose tolerance test (OGTT) GH >1.0 µg/L, and IGF-I level was above the upper normal range for age and sex. Patients were treated using transsphenoidal surgery performed by a senior neurosurgeon during period of 2015-2019. IGF-1 normalization was achieved in 6 out of 30 patients (20%) according to new consensus criteria (peak GH level during the OGTT of < 0.4 µg/L). All participants underwent an OGTT 3 months post-surgery and based on that peak GH level were divided into old consensus criteria (nadir GH level during the OGTT of < 1 µg/L or >1ug/L): the complete remission group or the not in remission group. Complete remission group was further divided according to a new consensus guideline into: the complete remission group and the partial remission group (postoperative nadir GH level during the OGTT of < 0.4 µg/L or ≥ 0.4 µg/L). We compared the clinical and biochemical characteristics, and postoperative SF-36 scores between the two groups. We also did pre- and post-surgical hormonal profile and follow-up patients 3 monthly.

3. Survey Methods

We conducted thorough Clinical and biochemical examinations pre- and 3-month post- surgery. The validity and reliability of SF-36 have been already established in Indian population and has been used to assess health outcomes in several diseased population [10,11]. All 30 patients completed SF 36 quality of life questionnaire at the assessment. The quality-of-life questionnaire evaluates 12 items regarding a patient's general well-being, each item has multiple questions under it and all questions have 5 possible answers. All questions are scored on a scale of 1–5. The items are scored in various scales: physical functioning, daily activities, symptoms, social, psychological, general health perception, sleep, sexual health, pain, energy, body image and cognition. Higher the scores poor is the quality of life. We compared the pre- and post- operative quality of life questionnaire scores. All patients completed preoperative questionnaire. In this questionnaire, responses to questions around physical symptoms — My body has enlarged/ grown enormously — could be given as "not important", "slightly important", "important"," fairly important" or "very important". We also assessed the severity of obstructive sleep apnoea with the help of polysomnography which is shown by the apnoea hypopnea index (AHI).

4. Statistical Analysis

Subjects were divided based on remission criteria. Spearman correlation coefficients were calculated between the change in IGF-I levels and SF 36 scores. Non-parametric tests (Mann-Whitney U and Kruskal-Wallis one-way ANOVA) were performed to test the statistical significance of differences between different groups. All statistical analyses were performed with SPSS software and a $p<0.05$ was considered statistically significant. Informed consent was obtained from all the individual participating in study.

5. Results

Table 1 shows the baseline characteristics of individuals. A total of 14 males and 16 female individuals Patient with mean age of 44.5 years (21-67) and mean duration of symptoms7.6 years (4 years-15 years) were included. Dyslipidaemia was the most common co-morbidity (80%), followed by hypertension (73%) and diabetes (60%). Coronary artery disease was present in 8 (26%) patients at baseline with none of them having history of cerebrovascular accident or malignancy. Acral enlargement was the most common symptom (73%) followed by arthralgia and fatigue (66%) (Table 2). Hyperprolactinemia (53%) was the most common hormonal abnormality followed by low cortisol (40%), hypothyroidism(30%), hypogonadism (23%) and diabetes insipidus (10%) (Table 3).

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Pituitary macroadenoma was found in (83%), followed by microadenoma(10%) and empty Sella (6.6%). On immunohistochemistry 24 patients had somatotroph adenoma, 4 patients had mamo-somatotroph adenoma and 2 patients had pleurihormonal adenoma. All patients were treated with surgery for IGF-1 normalization. Preoperative mean stimulated GH level was 66.4±55.4 ng/ml (1.5-185) and postoperative stimulated GH was 6±4.9 ng/ml (0.1-16) which was significant (p-0.003). The preoperative IGF-1 levels ranged from 344.0 µg/L to 1400.0 µg/L (mean: 797.3 ± 275.1 µg/L). There was a significant reduction in postoperative serum IGF-1 levels (388 ± 200 µg/L, p -0.003). No significant change in proportion of patients with hypertension, diabetes mellitus, or hyperlipidaemia, AHI. Fewer patients required hormonal replacement post operatively at 12month (Hyperprolactinemia-8, Hypothyroidism-4, low cortisol-6, hypogonadism-5, diabetes insipidus-1). Figure 1 shows Preoperative and postoperative (12 month and 24 month) subscale scores. Preoperative physical functioning (PF), role physical (RP), general health (GH) was below the national standard value as indicated by the boxed value. Significant postoperative improvements were observed for the physical functioning (PF) (53±10.4 vs 60±8.7 vs 63.3±6.7, p<0.0001), role physical (RP) (50.1±8.7 vs 60±9.9 vs 60.8±13.3, p<0.0001), general health (GH) (47.5±8.3 vs 63.6±8.1 vs 62.1±8.8, p,0.001) and mental health (MH) (58±7.8 vs 64.8±6.8 vs 70±6, p<0.0001) scores but not in bodily pain (BP) (62.8±9.1 vs 63.5±9.2 vs 63.6±9.1, p-0.934), vitality (VT)(65.1±7.2 vs 65.3±7.1 vs 65.6±7.6, p-0.965), social functioning (SF) (64.6±7.7 vs 64.8±7.7 vs 65.8±7, p-0.969), role emotional (RE) (63.1±8 vs 63.3±7.6 vs 63.5±7.6, p-0.986). Figure 2 shows the preoperative and postoperative results of PCS, MCS, and RCS score. The baseline score was close to the national standard. The PCS, MCS and RCS scores did change significantly after surgery. Figure 3 shows pre-operative and post-operative subscale score in patient group. There was significant difference in subscale score between partial and complete remission group in role physical (RP) (57.6±12.7 vs 71.4±9.8, p-0.014), social function (SF) (63.4±7.8 vs 70.7±6, p-0.05) and mental health (MH) (68.4±5.7 vs 75±4, p-0.009). Similarly, PCS (64.2±4.4 vs 67.5±4.6, p<0.012) and RCS (60.9±5.4 vs 69.2±5.4, p<0.0001) score significantly different in partial and complete remission group than MCS score (62.7±5.3 vs 67.1±5, p-0.064).

Table 1. Table showing baseline characteristics with radiological and immunohistochemistry character of individuals

Baseline Characters	N-30
Male: Female	14:16
Age(years)	44.5 (21-67)
Duration of symptoms(years)	7.6 (4-15)
Adenoma characteristics	
Macroadenoma	25(83%)
Microadenoma	3(10%)
Empty sella	2(6.6%)
Immunohistochemistry hormonal secretion	
GH Secreting	24(80%)
GH+Prolactin	4(13.3%)
Pleurihormonal	2(6.6%)

Table 2. Showing predominant symptoms in individual patients

Symptoms(N-30)	Number of patients
Acral enlargement	22(73%)
Coarse facial features	18(60%)
Hoarse voice	16(53%)
Excessive sweating	16(53%)
Arthralgias	20(66%)
Sleep apnoea	14(46%)
Headache	12(40%)
Hypogonadal symptoms	8(26%)
Visual deficit	10(33%)
Fatigue	20(66%)

Table 3. Showing predominant hormonal abnormality in individual patients

Hormonal abnormality(n-30)	Number preoperative	Number postoperative
Hypothyroidism	9(30%)	4(13%)
Hypocortisolism	12(40%)	6(20%)
Hypogonadism	7(23%)	5(16%)
Hyperprolactinemia	16(53%)	8(26%)
Diabetes Insipidus	3 (10%)	1(3%)

Table 4. Showing preoperative and postoperative characteristics of patients

Characteristics	Preoperative	Postoperative (12 month)	p value
Diabetes Mellitus	18(60%)	14(46%)	-
Hypertension	22(73%)	20(66%)	-
Dyslipidaemia	24(80%)	20(66%)	-
OSA	16(53%)	11(36%)	
Mild (AHI:5-20)	8(50%)	5(45%)	-
Moderate (AHI:20-40)	4(25%)	4(36%)	
Severe (AHI>40)	4(25%)	2(18%)	
CAD	8(26%)	8(26%)	-
CVA	0	-	-
Cancer	0	-	-
GH (Glucose stimulated)	66.4±55.4 ng/ml	6±4.9 ng/ml	0.003
IGF 1	797.3 ± 275.1 µg/l	388 ± 200 µg/l	0.003

OSA(Obstructive sleep apnea), CAD(Coronary Artery Disease), CVA(Cerebrovascular accident)

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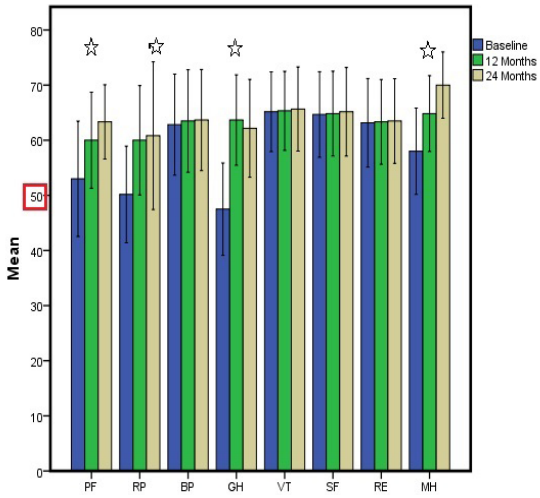

Figure 1. Showing preoperative and postoperative subscale score

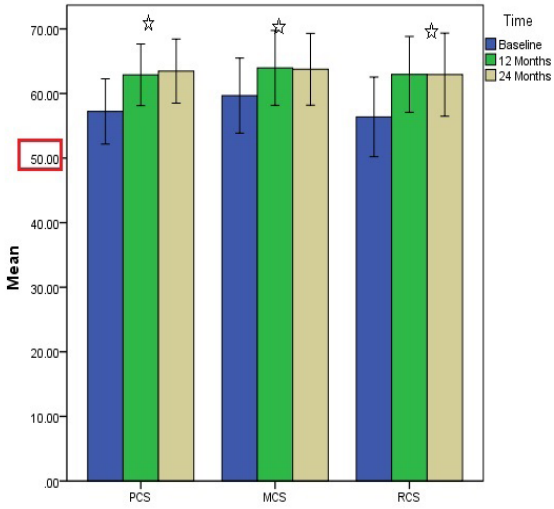

Figure 2. Showing preoperative and postoperative component score

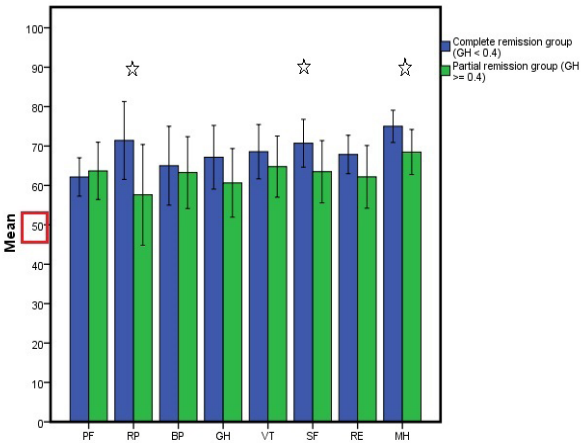

Figure 3. Showing subscale score in complete and partial remission group

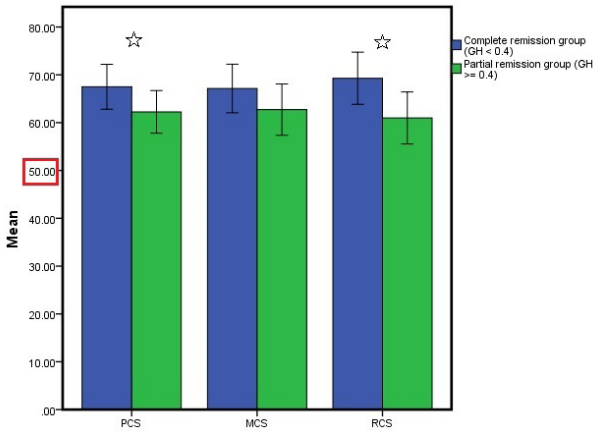

Figure 4. Showing component score in partial and complete remission group

6. Discussion

Acromegaly is associated with various disabilities with poor quality of life. There are very few prospective studies reporting postoperative changes in QOL among patients treated by surgery alone.

Our study showed preoperative SF-36 scores were lower in acromegaly patients than that of the general population in subscales, including physical functioning, role physical, general health which indicate that acromegaly significantly affects patient's physical condition, self-perception as well as participation. We found that postoperative there was significant improvement in physical component, mental component and role social component of SF36 QOL questionnaire. Sardella et al. [12] on the other hand found that surgical cure resulted in improvements in the mental components as compared to physical or role-social components of SF 36 QOL questionnaire. Yoshida et al. [13] in acromegaly patients reported higher psychological scores in patients with surgically achieved disease control. Biermasz et al. [14] found better physical function in surgically cured acromegaly patients.

Shingo Fujio [15] using SF-36 questionnaire found MCS score improved significantly postoperatively while there was no significant difference in PCS, RCS and MCS scores between complete and partial remission groups. We, on the contrary found that there was significant postoperative improvement in PCS, RCS and MCS scores but MCS score did not change significantly between complete and partial remission group.

All of our patients achieved IGF-1 normalization by surgery alone, and fewer number of patients required postoperative hormone replacement therapy. Several comorbidities, such as joint pain due to severe arthritis, myopathy and hypertension, impairs postoperative improvement

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in physical and emotional subscale score in some patients with acromegaly even after achievement of postoperative cure.

Gilbert et al. [16] in his study showed improvements in health perception and fatigue during medical treatment among newly-diagnosed with acromegaly. In addition, Sardella et al. [12] in Acromegaly patients observed improvements in psychological and appearance domains after a 6-month course of a somatostatin analog. Matta et al. [17] reported higher AcroQoL psychological subscale scores in controlled acromegaly patients compared to patients with uncontrolled disease.

There was significant difference in subscale score between partial and complete remission group in role physical (RP), social function (SF) and mental health (MH). In a similar study Renata Aparecida Elias Dantas [18] in acromegalic patients found the scores obtained on SF-36 domains were higher in patients with controlled disease and statistical differences were found in the domains Role Physical, Pain, Vitality, Role Emotional.

Kauppinen Mäkelin et al. [19] in his study reported that a post OGTT nadir GH level in the 0.3– 1.0 µg/L range could achieve the best QOL but not < 0.3 µg/L. Post OGTT nadir GH level <0.3 µg/L might have GH deficiency and adversely affect QOL. None of our patients developed post OGTT low GH suggestive of GH deficiency although we could not perform GH secretory function in our patient group.

Significant number of patients present with diabetes mellitus, hypertension and hyperlipidaemia pre-operatively which decreased post-surgery. However, the dose of antidiabetic and antihypertensive medication decreased in some cases but antihypertensives could not be withdrawn which could be due to irreversible remodelling of vascular system.

Small sample size has limited the generalization of our study. We need large studies to evaluate the effects of the surgical remission on the QOL of patients with acromegaly.

Some of the limitations of our study are, we have used SF-36 questionnaire which may be less sensitive when compared with disease-specific questionnaires, such as the AcroQoL questionnaire. OGTT will change depending upon the time of its performance [20]. We have performed OGTT at 3 months interval which could be different at 1 year when we administered SF36 questionnaire. We have evaluated SF 36 scores at baseline, 1 year and 2 years post-surgery but patient's score can change at any time. Therefore, long term studies with extended follow-up is needed to confirm the long-term effects of surgery. Finally, further studies are needed to gather information regarding the impact of GH deficiency on postoperative QOL.

7. Conclusions

Acromegaly is debilitating illness with multisystem involvement and poor QOL. Our study showed that acromegaly leads to low preoperative SF-36 QOL scores compared to the general population. Surgical remission leads to an improvement in the mental, physical and social domain of SF 36 QOL scores. There were significant differences in physical and social scores of QOL between complete and partial remission group. Although, small sample size has limited the generalisation of the finding of our study, there are few prospective studies reporting postoperative changes in QOL among patients cured solely by surgery. We need further large-scale long-term studies with extended follow-up to evaluate the effects of surgery as well as newer stricter remission criteria on QOL.

Contributor Ship Statement

Dr Dipti Sarma developed the research concept presented here along with Dr Manoj Gedam. Dr Manoj contributed to the study design and managed the database, participated in the data analysis. All authors have read and approved the final draft of the manuscript.

Conflict of Interest

No conflict of interest.

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Patient Consent

Informed verbal consent was obtained from the patient or primary caregiver.

References

[1] Arita K, Kurisu K, Tominaga A, Eguchi K, Iida K, et al. (2003) Mortality in 154 surgically treated patients with acromegaly: a 10-year follow-up survey. Endocr J 50: 163-172.

[2] Beauregard C, Truong U, Hardy J, Serri O (2003) Longterm outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 58: 86-91.

[3] Holdaway IM, Rajasoorya RC, Gamble GD (2004) Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 89: 667-674.

[4] Fatti LM, Scacchi M, Pincelli AI, Lavezzi E, Cavagnini F: Prevalence and pathogenesis of sleep apnea

  DOI: https://doi.org/10.30564/jer.v3i2.3531

and lung disease in acromegaly. Pituitary 2001, 4, 259–262.

[5] Orme SM, McNally RJ, Cartwright RA, Belchetz PE: Mortality and cancer incidence in acromegaly: a retrospective cohort study. J Clin Endocrin.

[6] Campbell PG, Kenning E, Andrews DW, Yadla S, Rosen M, et al. (2010) Outcomes after a purely endoscopic transsphenoidal resection of growth hormone-secreting pituitary adenomas. Neurosurg Focus 29: E5.

[7] Gondim JA, Almeida JP, de Albuquerque LA, Gomes E, Schops M, et al. (2010) Pure endoscopic transsphenoidal surgery for treatment of acromegaly: Results of 67 cases treated in a pituitary center. Neurosurg Focus 29: E7.

[8] Jane JA Jr, Starke RM, Elzoghby MA, Reames DL, Payne SC, et al. (2011) Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. J Clin Endocrinol Metab 96: 2732-2740.

[9] Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, et al. (2010) A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 95: 3141-3148.

[10] Sinha R, van den Heuvel WJ, Arokiasamy P. Validity and reliability of mos short form health survey (sf-36) for use in India. Indian J Community Med 2013;38:22-6.

[11] Muniyandi M, Rajeswari R, Balasubramanian R, Nirupa C, Gopi PG, Jaggarajamma K, et al. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. Int J Tuberc Lung Dis 2007;11:887-92.

[12] Sardella C, Lombardi M, Rossi G, Cosci C, Brogioni S, et al. (2010) Short- and long-term changes of quality of life in patients with acromegaly: results from a prospective study. J Endocrinol Invest 33: 20-25.

[13] Yoshida K, Fukuoka H, Matsumoto R, Bando H, Suda K, et al. (2015) The quality of life in acromegalic patients with biochemical remission by surgery alone is superior to that in those with pharmaceutical therapy without radiotherapy, using the newly developed Japanese version of the AcroQoL. Pituitary 18: 876-883.

[14] Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, et al. (2004) Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. J Clin Endocrinol Metab 89: 5369-5376.

[15] Fujio S, Arimura H, Hirano H, Habu M, Bohara M, Moinuddin FM, et al. Changes in quality of life in patients with acromegaly after surgical remission – a prospective study using SF-36 questionnaire. Endocr J (2016) 64(1):27–38.
DOI: 10.1507/endocrj.EJ16-0182.

[16] Gilbert J, Ketchen M, Kane P, Mason T, Baister E, et al. (2003) The treatment of de novo acromegalic patients with octreotide-LAR: efficacy, tolerability and cardiovascular effects. Pituitary 6: 11-18.

[17] Matta MP, Couture E, Cazals L, Vezzosi D, Bennet A, et al. (2008) Impaired quality of life of patients with acromegaly: control of GH/IGF-I excess improves psychological subscale appearance. Eur J Endocrinol 158: 305-310.

[18] Dantas RA, Passos KE, Porto LB, Zakir JC, Reis MC, Naves LA. Physical activities in daily life and functional capacity compared to disease activity control in acromegalic patients: impact in self-reported quality of life. Arq Bras Endocrinol Metabol (2013) 57(7):550–7.
DOI: 10.1590/S0004-27302013000700009.

[19] Kauppinen-Mäkelin R, Sane T, Sintonen H, Markkanen H, Välimäki MJ, et al. (2006) Quality of life in treated patients with acromegaly. J Clin Endocrinol Metab 91: 3891-3896.

[20] Espinosa-de-los-Monteros AL, Mercado M, Sosa E, Lizama O, Guinto G, et al. (2002) Changing patterns of insulin-like growth factor-I and glucose-suppressed growth hormone levels after pituitary surgery in patients with acromegaly. J Neurosurg 97: 287-292.

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ARTICLE

Progesterone Receptor Antagonists – A Novel Treatment for Severe Hyponatremia from the Endocrine Paraneoplastic Syndrome

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ABSTRACT

Hyponatremia related to ectopic secretion of cancer cells of arginine vasopressin (AVP) or atrial natriuretic peptide (ANP) is most commonly caused by small cell lung cancer. The ideal treatment would be one that not only corrects the hyponatremia, especially if it is life threatening, but at the same time causes regression of the cancer, and thus improves both quality and length of life. As one is waiting for chemotherapy, surgery, or radiotherapy to decrease the cancer burden, tolvaptan has been used to correct the hyponatremia to improve symptoms or prevent death. Mifepristone, a progesterone receptor modulator/antagonist has been used to treat various cancers. The oral 200mg tablet was given to an 80-year-old woman who developed sudden extensive lung cancer with a serum sodium of 118 mmol/L. She refused chemotherapy but agreed to take mifepristone. The hyponatremia was completely corrected (145 mmol/L) within one month of treatment. She was in complete remission for 5 years and died not from lung cancer, but an acute myocardial infarction. Mifepristone may serve the purpose to not only quickly correct hyponatremia when it is related to an endocrine paraneoplastic syndrome, but also to provide improved quality and length of life.

1. Introduction

Lung cancer is one of the most common cancers to cause endocrine paraneoplastic syndromes [1]. When paraneoplastic syndrome occurs, the associated metabolic or endocrine disorder is related to the malignant tumor secreting hormones or peptides [2]. One of these paraneoplastic syndromes is hyponatremia related to inappropriate secretion of the anti-diuretic hormone (ADH), and thus the condition is called the syndrome of inappropriate anti-diuretic hormone (SIADH) [3-5].

The most common type of lung cancer associated with SIADH is small-cell lung cancer (SCLC) representing about 70% of the lung cancer cases (1). SIADH may be present in 7-16% of patients with SCLC [6,7]. Though non-SCLC (NSCLC) has also been associated with SIADH, it only accounts for 1% of the cases of SIADH resulting from a paraneoplastic syndrome [8,9].

Another paraneoplastic etiology for hyponatremia associated with lung cancer is the ectopic secretion of the atrial

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natriuretic peptide (ANP) [1,10]. Studies of SCLC cell lines have demonstrated that ectopic ADH, and ANP, are equally likely to be the cause of the hyponatremia, and not uncommonly both may be increased at the same time [10-12].

The prognosis for patients with lung cancer with hyponatremia is worse than those with normal serum sodium levels [13]. Serum sodium levels <125 mEq/L are associated with an extremely poor prognosis, with death generally within two weeks associated with severe brain edema that is associated with very low sodium levels with the resulting low plasma hypo-osmolarity leading to headache, memory impairment, generalized muscle weakness and associated fatigue, seizures, nausea, and psychiatric dysfunction progressing to coma and death [13,14].

Chemotherapy, possibly combined with surgery or radiotherapy, and supportive measures are the main treatment modality for hyponatremia associated with lung cancer [15]. If one achieves a remission following chemotherapy, there is a high success rate in correcting the hyponatremia. However, with tumor recurrence, the hyponatremia generally also returns [15]. In very rare circumstances, aggressive chemotherapy may be associated with marked hyponatremia related to sudden excessive release of stored ADH (otherwise known as arginine vasopressin AVP)) and ANP [16].

A case is reported of probable rapid onset very aggressive SCLC, with marked hyponatremia, who had quick resolution of the hyponatremia, not with chemotherapy, but with a progesterone modulator/antagonist.

2. Case Report

A 78-year-old woman was first diagnosed with chronic lymphocytic leukemia (CLL). Since she was asymptomatic, she was given no therapy but continued observation and evaluation by blood studies. With continued slow progression of leukocytosis (38,000) and mild thrombocytopenia, and with the development of some symptoms of dyspnea on exertion and weakness, her hematologist when she was age 80 decided to try treatment with oral chlorambucil.

Three days after starting the chlorambucil her clinical status significantly deteriorated with confusion, extreme weakness, and severe respiratory distress. Three months prior to her admission to the hospital for this acute decline in her health status, it was noted that she had mild hyponatremia of 130 mmol/L. On admission her serum sodium was life threatening at 118 mmol/L. By manipulating fluid intake and administration of electrolytes intravenously, her serum sodium increased to 122 mmol/L. Her serum PO2 on admission was 72 mmHg.

A chest x-ray revealed extensive pulmonary nodules with the radiologic diagnosis of metastatic lung cancer, or less likely, rapidly advancing lymphoma, as opposed to rapid progression of her CLL to a more acute leukemia process.

A biopsy of a pulmonary lesion with possible chemotherapy was recommended, but she refused this management. However, after a brief discussion, she agreed to be treated with oral mifepristone 200 mg/day as an outpatient. A compassionate use investigational drug approval (IND) was obtained from the United States Food and Drug Administration and her treatment was approved by the Western Institutional Review Board.

She clinically was much improved after two weeks of treatment. After one month of treatment her PO2 was 99-100 mmHg without supplemental oxygen. Her serum sodium level was normal at 145 mmol/L.

After 2 months of treatment her computerized axial tomography (CT-scan) showed mostly complete resolution of all of her lung nodules with those remaining much smaller.

Subsequent chest x-rays over the next 5 years continued to demonstrate no pulmonary nodules just a ground glass appearance to the lungs. Her PO2 and serum sodium were continually normal. Her CLL did seem to respond to the very short course of chlorambucil and the CLL just slowly progressed over these 5-year period requiring no additional therapy.

At age 85 while sleeping she had an acute myocardial infarction, and she was pronounced dead when she arrived by rescue squad to the hospital's emergency room.

3. Discussion

The radiologists and oncologist based on chest x-ray and CT scan were convinced that the woman was suffering from lung cancer, but rapidly advancing lymphoma was a much less likely possibility. However, without a pathological diagnosis, they could not determine if the woman was suffering from SCLC or NSCLC. However, based on the very rapid aggressive onset, and the fact that hyponatremia related to excessive secretion of AVP or ANP is much more common in SCLC vs. NSCLC (or lymphoma), her oncologist favored SCLC as her diagnosis.

It is not clear if the severe sudden drop in serum sodium was related to rapid advancing lung cancer, or did the chlorambucil treatment, which was given for CLL (and would not be a very effective treatment for lung cancer), caused cell lysis with acute release of AVP or ANP further exacerbating pre-existing SIADH from mild ectopic AVP or ANP release from lung cancer cells?

Mifepristone has been proven to be an effective treatment for advanced lung cancer providing significant improved quality and extension of life [17-19]. Mifepristone

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has provided similar benefits in patients with a variety of different advanced cancers [20-26]. The mechanism of action is thought to be secondary to its effect on blocking membrane progesterone receptors that are needed to make a protein called the progesterone induced blocking factor (PIBF) [27-31]. This PIBF protein is unique with no amino acid homology to any known protein, is needed by both the fetal-placental unit and cancer cells to proliferate, invade, tissue and escape immune surveillance, but is not essential for everyday life in people that are healthy [27-31].

Tolvaptan has been used to treat cancer patients with hyponatremia due to SIADH [32]. Tolvaptan is an oral selective V2-receptor antagonist [33]. AVP normally acts on V2 receptors in the renal collecting duct to promote free water absorption, thereby increasing extracellular fluid volume [34]. The continued upregulated expression of AVP in paraneoplastic SIADH leads to excessive dilution of free sodium which leads to the state of hyponatremia [34].

In the post-hoc analysis of the SALT-1 and SALT-2 trials, 7 of 8 taking tolvaptan normalized their serum sodium vs. 2 of 16 placebo controls [32]. A previous study found similar results [35]. Tolvaptan could be used concomitantly with mifepristone to try to get the hyponatremia corrected in case the mifepristone is not able to cause regression of that particular patient's cancer. In that case, the tolvaptan could be used with the drug of choice for treating that cancer.

Nevertheless, the best treatment for the hyponatremia is to correct the cause of ectopic production by cancer cells of AVP or ANP, since the obvious goal is to prolong and improve quality of life. Nevertheless, tolvaptan seems to be a reasonable short-term solution in case the person could die from the hyponatremia before regression of the cancer is obtained by mifepristone, chemotherapy, radiotherapy or immune therapy. Nevertheless, in the case reported here, rapid correction of the severe life-threatening hyponatremia related to SIADH was solely related to mifepristone therapy.

References

[1] Mazzone PJ, Arroliga AC. Endocrine paraneoplastic syndromes in lung cancer. Curr Opin Pulm Med. 2003 Jul;9(4):313-20.

[2] Efthymiou C, Spyratos D, Kontakiotis T. Endocrine paraneoplastic syndromes in lung cancer. Hormones (Athens). 2018 Sep;17(3):351-358.

[3] Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med. 1957 Oct;23(4):529-42.

[4] Vorherr H, Massry SG, Utiger RD, Kleeman CR. Antidiuretic principle in malignant tumor extracts from patients with inappropriate ADH syndrome. J Clin Endocrinol Metab. 1968 Feb;28(2):162-8.

[5] Amatruda TT Jr, Mulrow PJ, Gallagher JC, Sawyer WH. Carcinoma of the lung with inappropriate antidiuresis. Demonstration of antidiuretic-hormone like-hormone activity in tumor extract. N Engl J 1963269:544-9.

[6] List AF, Hainsworth JD, Davis BW, Hande KR, Greco FA, Johnson DH. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. J Clin Oncol. 1986 Aug;4(8):1191-8.

[7] Lokich JJ. The frequency and clinical biology of the ectopic hormone syndromes of small cell carcinoma. Cancer. 1982 Nov 15;50(10):2111-4.

[8] Monsieur I, Meysman M, Noppen M, de Greve J, Delhove O, Velckeniers B, Jacobvitz D, Vincken W. Non-small-cell lung cancer with multiple paraneoplastic syndromes. Eur Respir J. 1995 Jul;8(7):1231-4.

[9] Tho LM, Ferry DR. Is the paraneoplastic syndrome of inappropriate antidiuretic hormone secretion in lung cancer always attributable to the small cell variety? Postgrad Med J. 2005 Nov;81(961):e17.

[10] Kamoi K, Ebe T, Hasegawa A, Sato F, Takato H, Iwamoto H, Kaneko H, Ishibashi M, Yamaji T. Hyponatremia in small cell lung cancer. Mechanisms not involving inappropriate ADH secretion. Cancer. 1987 Sep 1;60(5):1089-93.

[11] Cogan E, Debième MF, Philipart I, Pepersack T, Abramow M. High plasma levels of atrial natriuretic factor in SIADH. N Engl J Med. 1986 May 8;314(19):1258-9.

[12] Donckier JE, Meunier HT, Ketelslegers JM, Lambert AE. Atrial natriuretic peptide and the syndrome of inappropriate secretion of antidiuretic hormone. Ann Intern Med. 1986 Nov;105(5):795-6.

[13] Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer. 2010 Apr;68(1):111-4.

[14] Yeung SC, Habra MA, Thosani SN. Lung cancer-induced paraneoplastic syndromes. Curr Opin Pulm Med. 2011 Jul;17(4):260-8.

[15] Hainsworth JD, Workman R, Greco FA. Management of the syndrome of inappropriate antidiuretic hormone secretion in small cell lung cancer. Cancer. 1983 Jan 1;51(1):161-5.

[16] Saintigny P, Chouahnia K, Cohen R, Pailler MC, Brechot JM, Morere JF, Breau JL. Tumor lysis associated with sudden onset of syndrome of inappropri-

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ate antidiuretic hormone secretion. Clin Lung Cancer. 2007 Jan;8(4):282-4.

[17] Check DL, Check JH: Significant palliative benefits of single agent mifepristone for advanced lung cancer that previously failed standard therapy. Med Clin Sci 2019;1(2):1-5.

[18] Check JH, Check D, Poretta T: Mifepristone extends both length and quality of life in a patient with advanced non-small cell lung cancer that has progressed despite chemotherapy and a check-point inhibitor. Anticancer Res 2019;39:1923-1926.

[19] Check DL, Check JH, Poretta T, Aikins J, Wilson C: Prolonged high-quality life in patients with non-small cell lung cancer treated with mifepristone who advanced despite osimertinib. Cancer Sci Res 2020;3(2):1-5.

[20] Check JH, Dix E, Cohen R, Check D, Wilson C: Efficacy of the progesterone receptor antagonist mifepristone for palliative therapy of patients with a variety of advanced cancer types. Anticancer Res 2010;30:623-628.

[21] Check JH, Dix E, Sansoucie L, Check D: Mifepristone may halt progression of extensively metastatic human adenocarcinoma of the colon – case report. Anticancer Res 2009 May;29(5):1611-1613.

[22] Check JH, Wilson C, Cohen R, Sarumi M: Evidence that mifepristone, a progesterone receptor antagonist can cross the blood brain barrier and provide palliative benefits for glioblastoma multiforme grade IV. Anticancer Res 2014;34:2385-2388.

[23] Check DL, Check JH, Poretta T: Conservative laparoscopic surgery plus mifepristone for treating multifocal renal cell carcinoma. Cancer Sci Res 2020;3(2):1-4.

[24] Check JH, Check D, Srivastava MD, Poretta T, Aikins JK: Treatment with mifepristone allows a patient with end-stage pancreatic cancer in hospice on a morphine drip to restore a decent quality of life. Anticancer Res 2020;40:6997-7001.

[25] Check JH, Check D, Poretta T, Wilson C: Palliative benefits of oral mifepristone for the treatment of metastatic fibroblastic osteosarcoma. Anticancer Res 2021;41:2111-2115.

[26] Check JH, Check D: Mifepristone may be the best single pharmaceutical agent for treatment of a variety of advanced cancers. Cancer Sci Res 2021;4:1-6.

[27] Check JH, Nazari P, Goldberg J, Yuen W, Angotti D: A model for potential tumor immunotherapy based on knowledge of immune mechanisms responsible for spontaneous abortion. Med Hypoth 57:337-343, 2001.

[28] Check JH, Dix E, Sansoucie L: Support for the hypothesis that successful immunotherapy of various cancers can be achieved by inhibiting a progesterone associated immunomodulatory protein. Med Hypoth 2009;72:87-90.

[29] Check JH, Cohen R: The role of progesterone and the progesterone receptor in human reproduction and cancer. Exp Rev Endocrinol Metab 2013;8:469-484.

[30] Check JH: The role of progesterone and the progesterone receptor in cancer. Expert Review Endo Metab 2017;12:187-197.

[31] Check JH, Check D: Therapy aimed to suppress the production of the immunosuppressive protein progesterone induced blocking factor (PIBF) may provide palliation and/or increased longevity for patients with a variety of different advanced cancers – A review. Anticancer Res 2019;39:3365-3372.

[32] Gralla RJ, Ahmad F, Blais JD, Chiodo J 3rd, Zhou W, Glaser LA, Czerwiec FS. Tolvaptan use in cancer patients with hyponatremia due to the syndrome of inappropriate antidiuretic hormone: a post hoc analysis of the SALT-1 and SALT-2 trials. Cancer Med. 2017 Apr;6(4):723-729.

[33] Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006 Nov 16;355(20):2099-112.

[34] Schrier RW. Vasopressin and aquaporin 2 in clinical disorders of water homeostasis. Semin Nephrol. 2008 May;28(3):289-96.

[35] Petereit C, Zaba O, Teber I, Lüders H, Grohé C. A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan. BMC Pulm Med. 2013 Aug 29;13:55.

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ARTICLE

An Update on Management of Nonalcoholic Fatty Liver Disease & Nonalcoholic Steatohepapititis is the Time Ripe for Achieving Resolution of NAFLD & NASH Soon

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ABSTRACT

We earlier reviewed how obesity has assumed an endemic/pandemic proportions that has resulted in escalating incidence and prevalence of associated escalating worldwide incidence of Metabolic Syndrome (MetS) with non alcoholic fatty liver disease (NAFLD), that is correlated with enhanced morbidity. Later we tried to detail how probiotics, L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, along with Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin, Vitamin D, Allyl Isothiocyanate (AITC), might aid in treating and understand the etiopathogenesis of NAFLD. The prevalence of NAFLD all over the world is approximately 25%, with that of non alcoholic steatohepapititis (NASH), varying from 1.5%=6.45%. Particularly NASH, specifically the ones associated with fibrosis possess a greater chance of generation of side effects that include progression to cirrhosis as well as liver-associated mortality. Despite an improvement was observed with vitamin E, Pioglitazone. liraglutide in histological appearance in liver randomized controlled clinical trials (RCT), at present no drugs exists that have received FDI approval for NASH. The aim of this review was to update the newer drugs getting evaluated, undergoing phase 2-3 trials. Currently there are Obeticholic acid, elafibranor, cenicriviroc, resmetriom, in addition to aramchol, that are the five agents that are getting analysed in big, histology dependent phase 3 trials. Hopefully within another 2-4 years, newer, efficacious drugs will be available for the therapy of NASH. Besides that a lot of phase 2 trials are continuing for different drugs. Further depending on outcomes of phase 2-3 trials, combination treatments are getting evaluated. For future therapeutic approaches would be made up of variations in NASH phenotypes, besides personalized approaches based on various NASH phenotypes in addition to response of every single patient. Further recently there were reports of utilization of curcumin with nonselective beta blocker for regression from cirrhosis (reviewed by us). Hopefully once there are approved therapies for NAFLD/NASH, we can work in that direction.

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1. Introduction

Earlier we have reviewed how obesity is assuming an endemic/pandemic proportions resulting in escalating incidence as well as Prevalence associated escalating worldwide incidence of Metabolic Syndrome (MetS) with Non alcoholic fatty liver disease (NAFLD) [1-9], that is correlated with enhanced morbidity [8]. We tried to detail how probiotics, L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, along with Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin, Vitamin D, Allyl Isothiocyanate (AITC), SGLT Inhibitors etc might aid in treating and understand the etiopathogenesis of NAFLD. By definition non alcoholic fatty liver disease(NAFLD), classificationcan be performed histologically into non alcoholic fatty liver or non alcoholic steatohepapititis (NASH). The prevalence all over the world is escalating, being approximately 25%, with that of NASH varying from 1.5%-6.45% [10]. The cases of NASH particularly the ones with fibrosis posseses greater chances of side effects like cirrhosis as well as fibrosis–associated mortality [11-13]. The maximum significant histological parameter of NAFLD correlated with long time mortality is fibrosis (stage 2-4) [12,14]. Hence of these 2 surrogate endpoints require to get validated in phase 2b or 3 trials for the conditional passing of the drug for generation: i) rectification of NASH without deterioration of fibrosis or; ii) fibrosis getting decreased by 1 or > stages without deterioration of NASH [15]. Despite no FDA approved drugs for NASH, vitamin E, Pioglitazone, along with Liraglutide escalated liver histology of patients with NASH in randomized controlled clinical trial [16-18]. In spite of Vitamin E possessing potential advantages, it has been correlated with contradictory outcomes of total mortality [19], the haemorrhagic stroke [20] as well as prostate cancer in males >than 50 years age [21]. Pioglitazone results in weight escalation [16], with its utility in NASH still getting evaluated although now Sodium–glucose cotransporter 2 (SGLT2) inhibitors are being evaluated in view of lack of above limitation, hence adversities need to get balanced with the potential advantages in NASH patients [reviewed by us], having no other option for therapy besides lifestyle changes. Currently weight reduction as well as lifestyle changes with the utilization of diet as well as exercise is advocated as the 1st line treatment [22,23]. Nevertheless, long time compliance with lifestyle changes is tough for sustenance in target population. Thus, a main requirement that has not been resolved for a new agent is to resolve NASH along with reversal of liver fibrosis are present. The current major targets for NASH treatment are these: i) bile acid pathway, insulin resistance (IR), inflammation, Thyroid hormone receptor (THR)-β stimulation, hepatic lipid metabolism, antifibrosis etc. 5 Pharmacologic drugs: i)Obeticholic acid (OCA; Farsenoid X receptor [FXR] agonist); ii) Elafibranor (a Peroxisome Proliferator Activated Receptor [PPAR] α as well as δ agonist); iii) cenicriviroc (CVC-a dual antagonist of C-C chemokine receptor (cenicriviroc CCR) types 2 as well as 5; iv) resmetriom (THR-β- agonist) as well as aramchol (stearoyl-Co A desaturase [SCD1 inhibitor-resulted in enhancement of liver histology in phase 2 studies [24-28] along with are going through evaluation of their long term effectiveness as well as safety. In addition a lot of innovative agents that target NASH-associated pathways that are undergoing phase 1 as well as 2 trials are about 200 in number. Pharmacologic drugs are being analysed for NASH therapy. Here we review the mode of action of maximum Pharmacologic drugs that are significant as well as describe the key phase 2 as well as 3 studies which got finished or are still ongoing.

2. Classification of the Agents Dependent on the Mode of Action

2.1 AObeticholic Acid (OCA; Farsenoid X receptor [FXR] agonist)

OCA is obtained from the primary human bile acid, chenodeoxycholic acid, that is a natural Farsenoid X receptor [FXR] agonist [29]. FXR is a nuclear receptor which gets significantly expressed in the liver along with small intestine, having a significant part in the generation in addition to enterohepatic circulation of bile acids (Figure 1) [30,31]. Stimulation of FXR decreases bile acids generation by hampering the transformation of cholesterol to bile acids, as well as it has anti-inflammatory along with anti-fibrogenic action [32]. Stimulation of FXR in the ileum further hampers the uptake of bile acids by resulting in downregulation of Sodium dependent bile acid transporter. Lastly, OCA influences anticholestatic as well as hepatoshielding action by controlling the metabolism of cholesterol as well as bile acids [33].

In a phase 2a Clinical trial over OCA, patients with type 2 Diabetes mellitus (DM) as well as NAFLD were randomly divided to groups receiving 25 mg OCA (n=20), or groups receiving 50 mg OCA (n=21) or groups receiving placebo (n=23) once/day for 6 weeks (NCT00501592) [34]. Enhancement of insulin sensitivity occurred by 24.5 (p=0.011) in the combined OCA groups, while a reduction by 5.5% occurred in the placebo group. Significant decrease in the amounts of γ glutamyl transferase (γGT) as well as alanine amino transferase (ALT). Further occurred in the OCA groups, besides dose-associated weight reduction. Further, a significant reduction in the amounts of liver fibrosis markers were observed in the OCA groups

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receiving 25 mg. In a phase 2b clinical trial, noncirrhotic patients with NASH had a random division into 1:1 to groups receiving placebo (n=142) as well as 25 mg OCA (n=141) once/day for 72 weeks (FLINT NCT012605498) [24]. Fifty (45%) of the 110 patients in the OCA groups displayed enhancement of liver histology in contrast to 23 (21%) of 109 patients in the placebo group (RR,1.9; 95% Confidence interval [CI], 1.3-2.8P=0.0002). Further 2.3% of the OCA groups had pruritus occurring in contrast to 6% the placebo group. Enhancement of histological parameters of NASH, nevertheless, its long time advantage as well as safety requires more elaboration.

During the interim evaluation of an ongoing, phase 3 study of OCA, patients with NASH, an NAFLD activity score (NAS) of a minimum of 4, as well as fibrosis stage F2-F3, or F1 with a minimum of one associated comorbidity got randomly divided to into 1:1:1 ratio for getting placebo, OCA 10 mg or OCA 25 mg (GENERATE, NCT02548351) [35]. The primary evaluation implicated 931 patients with stage F2-F3 fibrosis (311 in the placebo group, 312 in the OCA 10 mg group as well as 308 in the OCA 25 mg group). The fibrosis escalation endpoint was attained by 37 (12%) patients in the placebo group, 55 (18%) in the OCA 10 mg group (p=0.045), as well as 71 (23%) in the OCA 25 mg (P=0.0002). The resolution point in NASH was not reached. Nevertheless, the outcomes of this interim evaluation demonstrated that, OCA 25 mg resulted in significant ameliorated fibrosis along with crucial constituents of NASH action.

The safety population (1968 patients with fibrosis stage F2-F3) belonging to this trial, the commonest side effect was pruritus, that took place in 5% of the OCA 25 mg group, 28% of the OCA 10 mg group, as well as 19% of placebo group. Mostly pruritus was of mild moderate degree. Nevertheless, 9% of OCA 25 mg safety population omitted the drug secondary to pruritus. The lipoprotein profile was further watched in the safety population. The average low density lipoprotein (LDL) cholesterol as well as total cholesterol amount reached maximum amounts at 3 months in the OCA group. Further 17% of the OCA group as well as 7% of the placebo group required statin therapy.

A phase 2 trial (CONTROL, NCT02633956) that tried to analyse the utilization of OCA in combination of statin therapy for NASH demonstrated that utilization of OCA at 5, 10 or 25 mg/day escalated the LDL-C amounts following 4 weeks of therapy along with atorvastatin supplementation resulted in reduction of LDL-C amounts lower than baseline in each OCA group by 8th week [36]. OCA combination with atorvastatin was usually safe in addition to having a good tolerance.

This OCA use has further been expanded to cirrhosis, as well as a phase 3 trial of OCA in patients with compensated cirrhosis secondary to NASH is ongoing. Patients got randomly allotted to 1:1:1 to the groups receiving OCA 10 mg, 10 mg with titration to 25 mg OCA at 3 months, or placebo for 18 months (REVERSE, NCT03439254). In the REVERSE study utilization of dose enhancement strategy is done in view of hepatic decompensation resulting in patients where cholestatic liver disease is markedly advanced that gets therapy with OCA [37]. The primary end point is the percentage of cases showing benefit in fibrosis by a minimum of 1 stage without any deterioration of NASH.

2.2 Non Bile Acid [FXR] Agonist

i) Tropifexor(LIN-452)

Tropifexor (TXR; LIN-452) represents a significantly potent. Non bile acid FXR agonist, which stimulates the expression of target genes at minimal dosage without any important Takeda G-protein coupled receptor clones 5 getting stimulated [38]. A phase 2 trial on TXR in NASH patients for 48 weeks is going on (FLIGHT-FXR, NCT02855164) [39]. During an interim evaluation of an ongoing trial for 12 weeks, akin to that of OCA, TXR illustrated lipid alterations that were not favourable with a dose-associated escalation in the LDL-C amounts as well as a reduction in the high density lipoprotein cholesterol (HDL-C) amount, besides pruritus, at greater dosages in contrast to placebo. Further a relative reduction in the liver fat amounts by magnetic resonance imaging (MRI) protein density fat fraction (MRI-PDFF) of -9.8% in placebo, -16.9% with TXR 60 mg , as well as -15.6% with TXR 90 mg, in the interim evaluation. More evaluation illustrated that TXR possessed greater benefit in patients possessing a lesser body mass index (BMI), which pointed that a weight dependent strategy, might be essential [40].

ii) Cilofexor (GS-9674)

With OCA possessing troublesome adverse actions like pruritus, hyper cholesterolemia, in addition to hepatic decompensation, selective, non bile acid synthetic FXR agonists have got generated. Cilofexor (GS-9674), represents a potent, nonsteroidal FXR agonist which basically works by stimulation of FXR in the intestine as well as don't go through enterohepatic circulation [41]. FXR agonism in the intestine by Cilofexor amplifies the physiologic liberation of fibroblast growth factor (FGF) 19, as well as might ameliorate the harmful actions of the systemic FXR stimulation, that are dyslipidemia. Pruritus hepatotoxicity [41]. 10 subjects of NASH as well as fibrosis stage F2-F3 in a

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proof of concept study received 30 mg/day of Cilofexor for 12 weeks documented reduction of hepatic fat amounts as well as stiffness, along with enhancement of liver biochemistry [42].

In a phase 2 trial 140 non cirrhotic as well as NASH patients got randomly allotted to Cilofexor 100 mg (n=56), Cilofexor 30 mg (n=56), or placebo (n=28) for 24 weeks (NCT02854605) [43]. The outcomes pointed that Cilofexor 100 mg resulted in reduction in the hepatic fat amounts, along with had reasonable enough tolerance. Commonly Pruritus was not encountered, but had a greater frequency in 100 mg (14%) vis a vis 30 mg (4%) Cilofexor as well as placebo groups (4%). No variation in Pruritus was encountered at the Cilofexor 30 mg in contrast to placebo, however, like a lot of other FXR agonists, Cilofexor resulted in Pruritus in a dose based method, with greater moderate –severe Pruritus in the ones getting 100 mg dose in contrast to placebo. Cilofexor for 24 weeks led to a significant decrease in hepatic steatosis, liver biochemistry, as well as serum bile acids in NASH patients. Other FXR agonists (nidufexor) [44], as well as EDP-305 [45] have got generated, being in phase 2 trials.

2.3 Fibroblast Growth Factor 19 (FGF19Analogue), NGM 282

The FGF family of hormones modulates metabolic functions in addition to tissue repair as well as regeneration [46]. FGF19 represents a downstream target of FXR getting activated, as well as FXR results in FGF19 liberation via the intestine. FGF19 is a hormone that is controlling bile acids generation along with glucose homeostasis [47], whereas NGM 282 is an artificially generated FGF19Analogue (Figure 1).

During a phase 2 study having 82 patients that had bi-

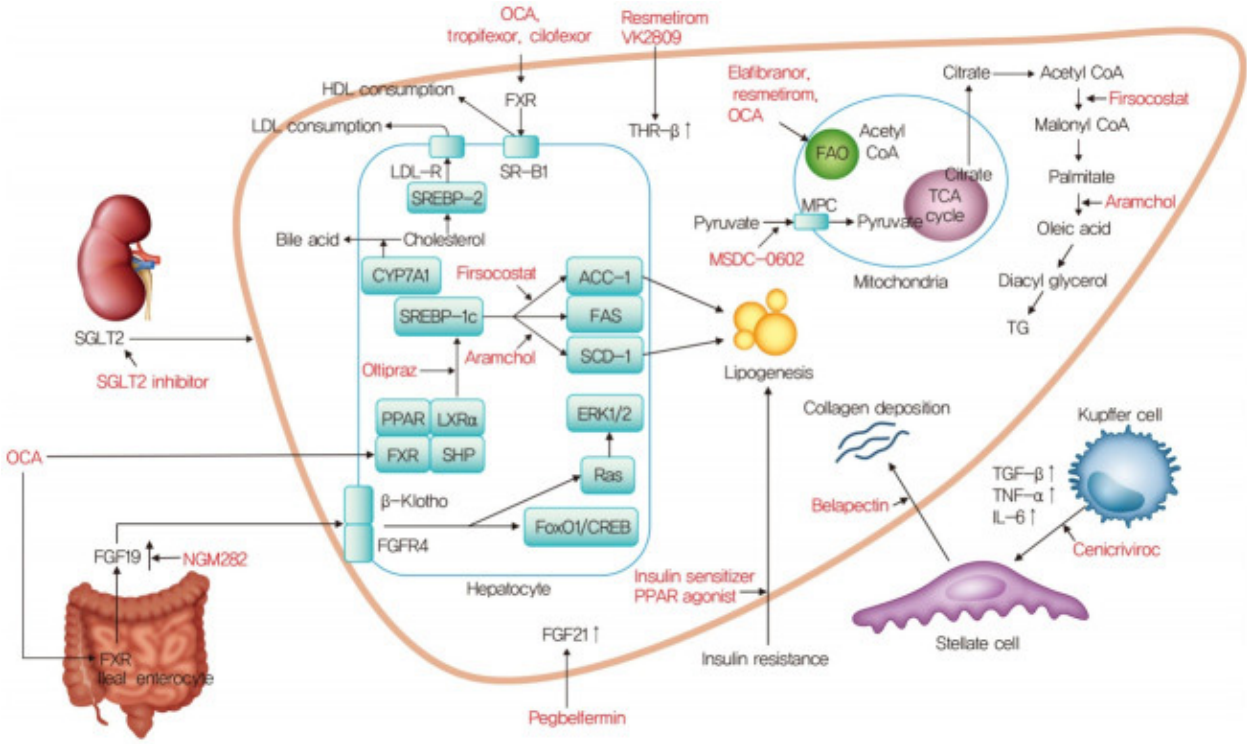

Figure 1. Fibroblast Growth Factor 19 (FGF19Analogue), NGM 282

Courtesy ref no 31-Mechanism of action for nonalcoholic steatohepatitis treatment. OCA, obeticholic acid; HDL, high density lipoprotein; LDL, low density lipoprotein; SGLT2, sodium glucose cotransporter 2; FXR, farnesoid X receptor; THR-β, thyroid hormone receptor-β; LDL-R, low density lipoprotein receptor; SR-B1, scavenger receptor class B type 1; SREBP-2, sterol regulatory element-binding proteins-2; CYP7A1, cholesterol 7α-hydroxylase; SREBP-1c, sterol regulatory element binding protein-1c; ACC-1, acetyl-coenzyme A carboxylase-1; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; PPAR, peroxisome proliferator-activated receptor; LXRα, liver X receptor α; SHP, small heterodimer partner; ERK1/2, extracellular signal-regulated kinase 1/2; FGFR4, fibroblast growth factor receptor 4; FoxO1, forkhead box protein O1; CREB, cAMP response element-binding protein; FGF, fibroblast growth factor; FAO, fatty acid β-oxidation; CoA, coenzyme A; TCA, tricarboxylic acid; MPC, mitochondrial pyruvate carrier; TG, triglyceride; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

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opsy validated NASH got randomly allotted to get 3 mg (n=27) or 6 mg subcutaneous NGM 282 (n=28) or placebo (n=27) (NCT02443116) [48]. The primary end point was the sheer alteration in liver fat amounts from baseline till week 12. Definition of responders were patients attaining a 5% or higher decrease in sheer liver fat amounts as estimated by MRI-PDFF. Subsequent to 12 weeks, 20 (74%) patients in the 3 mg groups as well as 22 (79%) in the 6 mg groups attained a minimum of 5% decrease in sheer liver fat amounts from baseline vs 2 (7%) in the placebo groups. NGM 282 generated fast as well as significant decrease in sheer liver fat amounts with the safety parameters that could be accepted in NASH patients. The histological efficiency of NGM 282 in a recent open label evaluation, in biopsy validated NASH was evaluated [49].

Paired liver biopsies from 43 patients delivered subcutaneous NGM 282 (1 mg; n=24; 3 mg, n=19) once/day for 12 weeks got assessed, that were blinded to time point, subject as well as clinical knowledge. At 12th week, NGM 282 enhanced the histological parameters of NASH, with important decreases in the NAS along with fibrosis scores, that was correlated with enhancement in noninvasive imaging in addition to serum markers. A larger phase 2 study possessing a target of 250 enrolled biopsy validated NASH is presently enrolling in an active manner (NCT02443116).

2.4 Pegylated Fibroblast Growth Factor 21, Pegbelfermin (MBS-986036)

Fibroblast growth factor 21 (FGF21) has further been believed to be a part of bile acid pathway. Stimulation of FXR in addition to PPARα, results in hepatic expression as well as liberation of FGF21 [50]. FGF21, that represents a nonmitogenic hormone, that is a crucial controller of energy metabolism [52]. Endogenous FGF21 possesses a small half life of 1-2 h, but utilization of different manipulation approaches have aided in generation of FGF21 analogues that possess a longer half life. Pegbelfermin (MBS-986036), represent a polyethylene glycol that has been a conjugated recombinant analogue of Fibroblast growth factor 21 that possess a longer half life which aids in weekly dosing.

In a randomized, double blinded, placebo-controlled phase 2a trial, 75 patients having a minimum BMI of 25 kg/m^2, biopsy validated NASH (fibrosis stage 1-3) as well as liver fat amounts of a minimum of 10% by MRI-PDFF got randomized into 3 groups (25 patients to get 10 mg Pegbelfermin/day as well as in the groups getting 20 mg Pegbelfermin weekly in contrast to the placebo groups. Maximum side effects were mild, of which the commonest one was diarrhea in 8 (16%) of 49 patients who received Pegbelfermin. Pegbelfermin treatment for 16 weeks was usually well accepted as well as significantly led to a reduction in hepatic fat fraction in patients with NASH. At present 2 large trials in phase 2 (FALCON 1, n=160, FALCON 2, n=152) are ongoing for evaluation of the effectiveness in addition to safety of Pegbelfermin.

2.5 Insulin Resistance

i) Peroxisome Proliferator Activated Receptor (PPAR)-agonist

a) Elafibranor

PPARs represent nuclear Receptors that possess critical part in cellular events controlling metabolic homeostasis. Three kinds of nuclear Receptors isoform, PPARα PPARβ/δ as well as PPARγ, that get encoded by separate genes [54]. Elafibranor (GFT505) is a double PPARα as well as δ agonist, which controls the lipid along with insulin metabolism. Maximum PPARα expression occurs in the liver, whose activation is performed by hypolipidemic fibrates. PPARα has the role of regulation of the lipid flux in the liver via modulation of fatty acids (FA) as well as β oxidation along with results in enhancement of plasma lipids by reduction in the triglycerides amounts as well as causing escalation of HDL-C [55]. In reference to advanced NASH, the PPARα amounts are decreased, that return to normal subsequent to treatment as well as enhancement [56]. PPARδ (alias PPARβ) controls the metabolism in the liver as well as peripheral tissues. PPARδ agonists cause enhancement of FAtransfer in addition to oxidation, escalated the HDL-C amounts, as well as enhance glucose homeostasis as well as escalation of insulin sensitivity as well as hampering hepatic glucose output [57]. In a pilot trial, a selective PPARδ agonist, decreased hepatic fat amounts, as well as led to enhancement of insulin sensitivity along with plasma lipid amounts in addition to reduction in the γGT amounts [58].

From the phase 2b study, performed on Elafibranor patients presenting with NASH who were non cirrhotic got randomized into getting Elafibranor 80 mg (n=83), elafibranor 120 mg (n=91) or placebo groups (n=92)/day for 52 weeks (GOLDEN 505, (NCT01694849) [25]. The primary end point was NASH getting resolved without deterioration of fibrosis, with the utilization of protocol definition as well as modification of definitions. During an intention to treat evaluation, no important variations among the Elafibranor as well as placebo groups in the primary end point was observed. Nevertheless, in a posthoc evaluation of patients with NAS (≥4) (n=234), elafibranor 120 mg demonstrated resolution of NASH in a larger percentage of patients in contrast to placebo,

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dependent on the definition of protocol (20% vs 11%; odds ratio 3.16, 3.52; p=0.013). Further patients where elafibranor resulted in resolution of NASH. Subsequentl to receipt of Elafibranor 120 mg demonstrated reduction in liver fibrosis in contrast to those where no resolution of NASH resulted. The amounts of liver enzymes, lipids as well as systemic inflammation in addition to glucose profile illustrated significant reduction in the elafibranor 120 mg vis a vis placebo groups. Tolerance of Elafibranor was good without resulting in weight accretion or cardiac processes, although did lead to mild reversible enhancement of the serum creatinine amounts.

A phase 3 trial one Elafibranor comprising of 2000 NASH patients (NAS(≥4) with stage 2-3 fibrosis is ongoing (RESOLVE-IT, NCT02704403). The primary end points is the percentage of patients where resolution of NASH without deterioration of fibrosis resulted at 72 weeks. Further the trial did an analysis of a composite long term results, comprising all cause mortality, cirrhosis as well as liver associated results at 4 years. The trial got initiated in March 16 as well as the outcomes are expected in December 21.

b) Lanfibranor

Lanfibranor (IVA337) represents an agonist of all the 3 isoforms of, having a well balanced stimulation of PPARα as well as δ, along with part stimulation of PPARγ [59]. Whereas other PPAR agonists target 1 or 2 of the PPAR isoforms. Lanfibranor represents the lone pan PPAR agonists that is undergoing clinical generation.

In a phase 2b clinical trial conducted on lanfibranor (IVA337) in case of patients with NASH in addition to liver steatosis as well as moderate to robust necroinflammation without cirrhosis, 247 patients got randomized into getting Lanfibranor 800 mg, 1200 mg or placebo/day for 24 weeks (NATIVE, NCT03008070). The primary end point was a reduction from baseline in the SAF (steatosis, activity as well as fibrosis) activity score. The study got initiated in January 2017 as well as was over by March 2020. The early outcomes were anticipated in December 2020 first half.

ii) a.Glucagon like peptide 1(GLP-1) Receptor agonist-Semaglutide

No Pharmacological treatments have got proven for NASH in addition to T2DM. The major thing is to find the most appropriate anti diabetic agents for the therapy of NASH, for avoidance of the propagation of hepatic fibrosis as well as cardiovascular or renal processes. Glucagon like peptide 1 (GLP-1) Receptor agonist along with Sodium–glucose cotransporter 2 (SGLT2) inhibitors are anticipated to mitigate NASH in addition to NAFLD. GLP-1 represents a gut generated incretin hormone which stimulates reduction of weight of patients along with insulin sensitivity. GLP-1 analogues got approval for utilization in T2DM along with obesity. The advantages of these analogues are weight reduction, escalated glycaemic regulation, lesser hypoglycemia processes along with a decreased incidence of cardiovascular processes [60,61]. The part of GLP-1 in the management of NASH along with NAFLD appear lucrative [17,62,63].

In a recent randomized, placebo-controlled trial implicating 52 patients with biopsy corroborated NASH 1.8 mg of subcutaneous Liraglutide delivered/day for 48 weeks had a correlation with greater NASH resolution as well as lower propagation of fibrosis [17]. Nevertheless, the American Association for the study of liver disease practice guidance 2018 advocated that it was preterm to think of GLP-1 agonists for the treatment of liver disease in cases of NASH along with NAFLD [23].

Semaglutide represents a novel GLP-1 analogue that posseses a prolonged half life of about a week. During phase 2 study of the actions of Semaglutide on NASH, 320 patients with NASH got randomly allocated to placebo groups or 3 dosage amounts of Semaglutide by subcutaneous injection for 72 weeks (NCT02970942). The primary end point comprised resolution of NASH without deterioration of fibrosis. Early outcomes from the study were anticipated in May 2020. In a separate phase 2 study implicating weekly Semaglutide 2.4 mg x 48 weeks. The primary results are enhancement of amelioration of liver fibrosis by a minimum of a stage without deterioration of NASH following 48 weeks (NCT0387451). Semaglutide seems to be the one that is most attractive for the treatment of NASH correlated with DM. Nevertheless, if GLP-1 analogues escalated hepatic inflammation resolution or fibrosis in NASH is not clear as yet.

b) Dapagliflozin, a Sodium –glucose cotransporter 2 inhibitor

Sodium–glucose cotransporter 2 (SGLT2) inhibitors hamper glucose reabsorprtion in the proximal tubule, resulting in glucosuria, resulting in decrease of plasma glucose amounts. Hence, (SGLT2) inhibitors possess a treatment potential for both NASH along with NAFLD. Certain studies (small) have demonstrated the action of Dapagliflozin in case of patients with NAFLD as well as type2 Diabetes mellitus (T2DM) [64]. Despite the probability can't be ruled out that a fall in body

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weight or visceral adipose tissue (VAT) secondary to Dapagliflozin might be correlated with a reduction in hepatic steatosis or fibrosis, Dapagliflozin demonstrated an advantage in patients with NAFLD. A multicenter, randomized, placebo-controlled phase 3 Clinical trial is ongoing for evaluation of the effectiveness as well as safety of Dapagliflozin for the therapy of NASH (DEAN, NCT03723252). The primary end point is enhancement of the liver histological score at 12 month. 100 subjects with NASH got randomly allocated to placebo groups or10 mg of Dapagliflozin. This study got initiated in March 19, as well as outcomes awaited in November 21.

2.6 Mitochondrial Target of Thiazolidenedione-MSDC-0602K

1st generation insulin sensitizers thiazolidenediones have the ability to directly bind to as well as stimulate the PPARγ nuclear hormone Receptors as well as have got utilized for the treatment of T2DM [65]. Nevertheless, they are correlated with important adverse actions like edema, bone fractures that get modulated by PPARγ, along with hypoglycemia. The 2nd generation insulin sensitizer MSDC-0602K got fashioned for decreasing these adverse actions, whereas continuing to generate insulin sensitizing Pharmacology in case of animal models of DM [66], as well as NASH [67]. It manipulates the action of extra nutrition at mitochondrial pyruvate carrier (MPC) with least PPARγ binding (Figure 1) [68]. Earlier studies demonstrated, that MSDC-0602K had the capacity of enhancement of lipid oxidation, as well as diminish denovo lipid generation as well as gluconeogenesis in the liver, both in vivo, as well as in vitro, without adverse actions of the 1st generation insulin sensitizers [69].

During a randomized, double blinded, placebo-controlled phase 2b trial for 52 weeks patients with biopsy corroborated NASH as well as fibrosis (F1-F3) got a random allocation to placebo groups (n=94) or 62.5 mg (n=99), 125 mg, (n=98) or 250 mg (n=101) of MSDC-0602K (EMMINENCE, NCT02784444) [70]. The primary end point for effectiveness was the hepatic histological enhancement of ≥2 points in NAS with a ≥1point decrease in ballooning or lobular inflammation as well as no escalation in fibrosis stage at 12 months time duration. No significant influence on liver histology was observed in that particular study secondary to MSDC-0602K. Nevertheless, significant reduction in amounts of fasting blood glucose, insulin, glycated haemoglobin, as well as markers of liver damage without any dose restricting adverse actions. A phase 3 study was supposed to get started in 2020 (MMONARCh, NCT03970031).

2.7 Inflammation

i) C-C chemokine receptor CCR Dual types 2 as well as 5(CCR2/CCR5) antagonist (cenicriviroc)

CVC or cenicriviroc represents an oral double antagonist of CCR2 as well as CCR5. Once CCR2 gets blocked that represents a chemokine receptor that mainly gets expressed in monocyte, along with, macrophages, causes a reduction in monocyte, along with macrophages, their migration in addition to infiltration of these cells towards the damaged areas of the liver [71]. Simultaneous inhibition of CCR5 interferes with the migration, activation along with proliferation of the activated hepatic stellate cells [71].

During a phase 2b trial for CVC in case of patients with NASH (NAS≥4) with fibrosis (F1-F3), 289 patients got a random allocation to either CVC 150 mg or placebo groups. The primary end point decided was a ≥2 point enhancement in NAS in addition to no deterioration of fibrosis at 1 year (CENTAUR, NCT02217475) [26,72]. The primary end point of enhancement in NAS in the intention for treatment population as well as NASH resolution was attained in an akin percentage of cases on CVC (n=145) as well as placebo. Nevertheless, the fibrosis end point was achieved in greater amounts of cases on CVC in contrast to placebo (20% vs 10%, p=0.02). Therapeutic advantages were higher in those displaying greater disease activity in addition to fibrosis stage at baseline. Subsequent to 1 year of CVC therapy double the number of patients attained in fibrosis without deterioration of NASH in contrast to placebo.

AURORA (NCT03028740), a randomized, double blinded, placebo-controlled, multicenter, phase 3 trial is ongoing for evaluation of efficacy as well as safety of CVC therapy for liver fibrosis in 2000 subjects of NASH presenting with stage 2-3 fibrosis. This study is planned in 2 parts. Part 1 is meant for evaluation of the surrogate end point of enhancement in fibrosis with a minimum of one stage as well as without deterioration of NASH at 12 months. Those cases from part 1 would resume in part 2 in addition to further extra patients added would get re – randomized in part 2 for estimating the long duration clinical results - histopathological – propagation to cirrhosis, Liver-associated Clinical features, in addition to all cause Mortality. This trial got initiated in April 2017, with the outcomes anticipated in December 2024.

2.8 Thyroid Hormone Receptor β-agonist (THR-β-agonist)

Resmetriom (MGL-3196)

The Thyroid hormone Receptor (THR-β) gets signifi-

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cantly expressed in the hepatocyte. NASH may represent partially, a problem secondary to reduction of liver thyroid hormone amounts or hepatic hypothyroidism, along with the incidence of clinical as well as sub clinical hypothyroidism is greater in subjects with NAFLD or NASH in contrast to those age matched controls [73,74]. Activation of THR-β causes the advantageous metabolic actions on triglycerides as well as cholesterol amounts in addition to enhancement of hepatic steatosis [73]. Possessing the actions of beneficial cardiometabolic profile along with ameliorated hepatic steatosis, THR-β- agonist are getting evaluated for NASH therapy.

Resmetriom (MGL-3196) acts as a liver pointed, orally working selective THR-β- agonist fashioned to provide relief in NASH by escalation of hepatic fat metabolism as well as reduction in lipotoxicity. During a phase 2 study, patients having biopsy verified NASH (fibrosis stage 1-3) as well as hepatic fat percentage ≥10% by MRI-PDDF got a random allocation to 2:1 for getting Resmetriom 80 mg or matching placebo, orally once/day (NCT02912260) [27].

The primary results were the proportional alterations from baseline in hepatic fat percentage as evaluation done by MRI-PDDF at 12 weeks.A significant decrease in hepatic fat percentage following 12 as well as 36 weeks of Resmetriom was observed. Tolerance was good, nevertheless, it resulted in Gastrointestinal tract (GIT), side effects, that were self restricted as well as were not responsible for the study getting withdrawn.

A Phase 3 trial implicating 2000 patients with NASH along with stage 2.3 fibrosis is ongoing (MAESTRO-NASH, NCT03900429). The primary result is the action of Resmetriom 80 or 100 mg in contrast to placebo on liver histology along with a composite long duration results of the amount of patients with the initiation of any of the considered processes like cirrhosis, all cause mortality, as well as liver associated Clinical features. This trial got initiated in March 2019, with the outcomes anticipated in March 2024.

VK2809

VK2809 represents a small molecule product of a robust THR-β-agonist. VK2809 gets selectively cleaved in the Liver tissue by the enzyme cytochrome P450 isozyme 3A4, to liberate a pharmacologically active metabolite. During a Phase 2a trial, patients possessing a hepatic fat amounts of ≥8% as evaluation done by MRI-PDDF, a LDL-C amount of ≥110 mg/dl, along with a triglycerides amount of ≥120 mg/dl got a random allocation to get oral VK2809 5 mg/day, 10 mg alternate day, 10 mg/day or placebo for 12 weeks [75].

Significant drop in hepatic fat amounts by MRI-PDFF in contrast to placebo was documented in the patients getting VK2809. The median relative alteration from baseline in hepatic fat amounts was 53.8% for VK2809 5 mg/day (p=0.0001). 56.1% for 10 mg alternate day (p=0.0018) as well as 59.7 for 10 mg/day (p=0.0004) vs 9.4% for placebo.

Dependent on these outcomes, a Phase 2b study is ongoing in 337 subjects with biopsy validated NASH, for evaluation of the effectiveness along with safety of VK2809 (1.0,2.5,5.0,10 mg) vis a vis placebo for 52 weeks. The primary result is the relative alteration in hepatic fat amounts (evaluation by MRI-PDFF) from baseline to12 weeks (VOYAGE, NCT04173065). The study was initiated in November 2019.

2.9 Hepatic Lipid Metabolism

i) Stearoyl-Co A Desaturase (SCD1) Inhibitor-Aramchol

Aramchol represents arachidylamido cholanoic acid, that is an innovative synthetic lipid molecule, a conjugate of the bile acid, cholic acid as well as arachidic acid, a fatty acid. It results in transformation of saturated FAsinto monounsaturated FAs (Figure 1) [76]. Aramchol has been evaluated in a Phase 2a trial, over 3 months at doses of 100 mg as well as 300 mg/day. This study illustrated a decrease in hepatic fat by magnetic resonance spectroscopy (MRS) following 3 months of treatment in the 300 mg/day Aramchol group in contrast to placebo, but not in the 100 mg/day Aramchol group. Further a decrease in the ALT amounts, with the compounds being well tolerated [77]. Greater doses of Aramchol (400 mg/day-600 mg/day) were delivered to patients with biopsy validatedNASH (n=247) without cirrhosis in a Phase 2b trial which analysed their actions on liver triglycerides amounts with the utilization of (MRS) as well as liver biopsy (ARREST-NCT02279524) [28]. A significant ≥5% decrease in hepatic fat amounts was seen with 600 mg/day Aramchol, 47% in contrast to placebo, 24%. As per liver histology, NASH resolution without deterioration of fibrosis was observed in greater instances with 600 mg Aramchol in contrast to placebo (16.7% vs 5% OR, 4.74; 95% CI, 0.99-22.66). Despite the study being underpowered for histological evaluation a dose response pattern in favour of NASH resolution as well as fibrosis amelioration was observed. A Phase 3/4 multi nation-

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al, multicenter, double blinded, placebo-controlled study for analyzing the effectiveness along with safety of Aramchol in cases with NASH (fibrosis 2 or 3) who present as overweight or with obesity along with prediabetes or T2DM (ARMOR, NCT04104321) has been continuing since September 2019.

ii) LiverX Receptor-α inhibitor- Oltipraz

Oltipraz represents a synthetic dithiolethione which works as anti steatotic drug by hampering LiverX Receptor-α (LXR –α) activity (Figure 1) [78]. Dithiolethiones are an innovative class of adenine monophosphate activated protein kinase (AMPK) stimulators, that avoid insulin resistance (IR) by hampering AMPK-based p70ribosomal S6 kinase1 (S6K1). AMPK represents a serine/threonine kinase possessing a key part in the controlling of carbohydrates as well as fat metabolism, besides which it might result in modulation of LXR–α action along with causing a reduction in expression of sterol regulatory element binding protein 1c (SREBP1c), a crucial Controller of lipid generation [79]. Oltipraz has a treatment potential for steatosis by stimulation of AMPK in addition to hampering S6K1. Further it encourages lipid oxidation by hampering LXR–α action along with resulting in reduction in expression of SREBP1c in the liver [78]. A Phase 2 study is presently continuing in patients with hepatic fat amounts>20% as well as hypertransaminasaemia got random allocation to get placebo (n=22), 30 mg Oltipraz (n=22), 60 mg Oltipraz (n=24), bdx 24 weeks (PMK-N01GH, NCT01373554) [80]. The primary result was the alteration in the hepatic fat amounts as evaluated by MRS from baseline x 24 weeks.

In contrast to placebo groups, a significant reduction in the hepatic fat amounts was caused by Oltipraz in a dose–based manner. Nevertheless, the sheer alterations in IR along with the amounts of liver enzymes, lipids as well as cytokines were not significantly altered in any of the groups. Moreover the side effects were similar among the groups.

A multicenter, randomized, double blinded, placebo-controlled parallel, phase 3 Clinical trial is going on for analyzing the effectiveness along with safety of Oltipraz in 144 subjects with NAFLD (NCT04142749). The primary results is the difference in the amounts of liver fat as evaluated by MRS at 24 weeks in contrast to baseline. The study was initiated in December 2019, with early outcomes anticipated in October 21.

iii) Acetyl-CoA Carboxylase inhibitor, firsocostat (GS0976)

The Controlling of denovo lipogenesis (DNL) possesses a main part in the fatty acids (FA) generation along with their catabolism. The rate restricting step in DNL is transformation of Acetyl-Coenzyme A (Acetyl-CoA) to malonyl CoA by the enzyme Acetyl-CoA Carboxylase (ACC). ACC possesses 2 isoforms. The ACC 1isoform catalyzes the generation of malonyl CoA, that is the main substrate for the (FA) generation within the cytosol. ACC2 resides in the mitochondria, where malonyl CoA works as a robust allosteric inhibitor of carnitine palmitoyl transferase (CPT)1, that is the carrier protein of FA into mitochondria for the β oxidation [77,81]. Hampering of ACC 1 as well as ACC 2 would get anticipated to decrease DNL as well as a escalate mitochondria β oxidation, respectively, pointed that hampering of ACC would be a treatment target in NASH [82]. Firsocostat (GS0976) represents a liver targeted, small molecule allosteric *i*nhibitor of both ACC 1 as well as ACC 2 in the generation of NASH (Figure 1).

During a recent phase 2 trial, 126 cases with hepatic steatosis of ≥8% dependent on MRI-PDFF, as well as liver stiffness of ≥2.5 kPa, dependent on MRE, or biopsy that corroborated with NASH as well as F1-F3 fibrosis got a random allocation to (2:2:1) for getting GS0976 (20 mg), GS0976 (5 mg), or placebo groups day for 12 weeks. During that study, 20 mg delivery of GS0976 was safe along with resulted in significant decrease in liver fat amounts by MRI-PDFF as well as a reduction in TIMP1. That is a marker of fibrogenesis (NCT02856555) [83].

2.10 Anti Fibrotic Drugs

i) Galectin-3 inhibitor, Belamectin (GRMD-02)

Galectins represent carbohydrate-binding proteins that belong to the family of non-integrinβ-galactoside–binding lectins [84]. Galectin-3 (Gal-3) is the commonest Galectin liberated in disease, basically by macrophages. Gal-3 through its intracellular (antiapoptotic, macrophages differentiation) along with extracellular (chemokinetic as well as chemotactic factor) actions is significant to the pathophysiology of hepatic fibrosis that result secondary to a lot of chronic Liver diseases [85,86]. Galectin inhibitors represent a new class of drugs which target both liberated as well as membrane – correlated Galectins in view of their high molecular weight [87]. Belamectin (GRMD-02), represents galactoarabino-rhamnogalacturonate) is a complicated carbohydrate molecule obtained from anatural plant source, that possesses oligosaccharide chains having

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galactose residues as well as binds to the Galectin3 with a lesser amount to Galectin1. A phase 1 study has illustrated that Belamectin possesses good effectiveness along with safety at single along with multiple doses of 2, 4 as well as 8 mg/kgin patients possessing NASH having all properties of proved NASH in addition to advanced fibrosis but no cirrhosis [88].

During a multicenter, randomized double blinded, placebo-controlled phase 2b trial, 162 patients with NASH, cirrhosis as well as portal hypertension (with hepatic venous pressure gradient [HVPG]≥6 mmHg) got a random allocation to get biweekly infusion of Belamectin 2 mg/kg (n=54), 8 mg/kg (n=54), or placebo (n=54) for 52 week [89]. The primary end point was the alteration in HVPG (-28) by the finishing of 52 weeks duration in contrast to baseline. Despite belpectin being safe, it was not correlated with a significant decrease in HVPG or fibrosis, in contrast to placebo. Nevertheless in a subgroup evaluation of patients without esophageal varices, 2 mg/kg belapectin actually led to a reduction in the generation of varices. A phase 3 study for analyzing the safety along with effectiveness of belapectin for the avoidance of esophageal varices in case of as well as patients with NASH cirrhosis without esophageal varices is getting started (NCT 04365868).

3. Combination Treatment

NASH represents a multifactorial disease implicating various modes for its genesis with no definite approved treatments. In future combination of drugs are attractive in view of targeting a lot of pathways. Maximum drug combinations are constituted by metabolic, inflammatory as well as fibrotic drugs or as an other way an anti diabetic might be utilized. At present 3 Combination treatments options for NASH are there.

3.1 TXR as well as CVC

A randomized, double blinded, multicenter, placebo-controlled phase 2b study for patients evaluation of safety along with effectiveness of TXR as well as CVC IN 200 cases with NASH fibrosis (stage2/3) (TANDEM, NCT03517540) [90]. Randomization of patients in a 1:1:1:1 ratio for getting TXR 140 μg+CVC 150 mg once a day. The study is designed as a 48 week treatments time as well as 4 week follow up. The primary aim is analysis of safety along with tolerance of this combination treatments as compared to monotherapies over 48 weeks. The secondary aim is effectiveness that by definition is ≥1 point enhancement in liver fibrosis vis a vis baseline or resolving of steatohepatitis following 48 weeks. Thus this combination treatments targets steatotic, inflammatory as well as /or fibrotic pathways that are accountable for NASH.

3.2 Selonosertib, Firsocostat, as well as Cilofexor

A recent phase 2 study analysed safety along with effectiveness of a combination of Selonosertib, firsocostat, as well as cilofexor in patients with bridging fibrosis of compensated cirrhosis without deterioration of NASH. Results were anticipated in 2020.

3.3 Semaglutide, Firsocostat as well as Cilofexor

During a phase 2 study where utilization of combination of Semaglutide, firsocostat as well as cilofexor wasdone, 109 cases presenting with NASH fibrosis (stage 2/3) got a random allocation to Semaglutide groups, Semaglutide+ firsocostatgroup, Semaglutide+ cilofexor 30 mg group, Semaglutide+ cilofexor 100 mg, or Semaglutide + firsocostat + cilofexor group (NCT039U7074). The primary aim is analysis of safety along with tolerance of the study drug/drugs in adult cases with NASH.

3.4 TXR as well as Licogliflozin

Licogliflozin is a once/day, oral SGLT1/2 double inhibitor. A phase 2b randomized, double blinded, multicenter, study is doing evaluation of the safety along with effectiveness of as well as tolerance of oral TXR as well as licogliflozin in combination treatments in contrast to monotherapies, in case of subjects with NASH as well as liver fibrosis. The primary end point is the population of patients with NASH resolution by a minimum of one stage without deterioration of fibrosis at 48 weeks in contrast to baseline (ELIVATE, NCT 04065841).

4. Conclusions

Despite Vitamin E, pioglitazone, Liraglutide cause enhancement of liver histology, no FDA approved agent exist for NASH currently. Hence weight reduction by utilization of lifestyle modifications, that are diet along with exercise remains the major way of treatment of NAFLD. Here we have given an overview of the key phase 2-3 trials dependent on the mode of working in NASH (Figure 2).

5 Pharmacological drugs like Obeticholic acid, elafibranor, cenicriviroc, resmetriom, in addition to aramchol are getting analysed in big, histology dependent phase 3

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trials. Depending on the outcome of these trials, newer agents possessing greater efficacy are anticipated in 2 to 4 years. Various phase 2 trials are ongoing with different drugs like non bile acid Farsenoid X receptor antagonists, FGF19 along with 21 analogues, GLP-1RA, SGLT2 inhibitors, pan-PPAR agonists, MPC inhibitors. ACC inhibitors as well as Gal-3 antagonists. Combination treatments are further getting analyzed. In view of NASH occurring secondary to a lot of factors combination treatments appear to be promising. Lastly, finally further approaches of treatments would be composed of combination treatments along with precision medicine depending on the various phenotypes of NASH along with personalised patients treatment response.

Figure 2. key phase 2-3 trials dependent on the mode of working in NASH

Courtesy ref no 31-The classification of phase 2,3 trials based on mechanism of action in nonalcoholic steatohepatitis (NASH) treatment. FXR, farnesoid X receptor; FGF, fibroblast growth factor; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium glucose cotransporter 2; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MPC, mitochondrial pyruvate carrier; SCD1, stearoylCoA desaturase 1; ACC, acetyl-coenzyme A carboxylase; THR-β, thyroid hormone receptor-β.

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References

[1] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. A Mini Review on Development of Newer Therapies for Non Alcoholic Fatty Acid Liver Disease with Emphasis on Vitamin D and its Receptor and Allyl Isothiocyanate (AITC)". Acta Scientific Nutritional Health 2019; 3(12) :1-5.

[2] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An Update on Further Progression of NAFLD, NASH with Prospective Therapies Like L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, as well as Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin as Alternatives. Int J Clin Med Cases. 2020 Jan;3(3):138.
DOI: 10.31021/ijcmc.20203138-29/1/2020 jan 29.

[3] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Have Probiotics and Synbiotics passed the test of time to be implemented in management of obesity and related metabolic disorders-a comprehensive review. *Adv Obes Weight Manag Control*. 2019;9(1):21-28.
DOI: 10.15406/aowmc.2019.09.00269.

[4] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Will Probiotics Provide the Answer for Therapy of Non-alcoholic Fatty Liver Disease (NAFLD)? – A Systematic Review. Biochem Physiol 2020;9: 257.

[5] Kulvinder Kochar Kaur,Allahbadia GN,Singh M.. Rosmarinic Acid-A New Hope for Liver Diseases Like Cirrhosis, Hepatocellular Carcinoma-NeedsTranslation to Humans". EC Endocrinology and Metabolic Research 2019;4(6): 289-301.

[6] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How do we apply advances in knowledge of Hepatic Macrophages in treating Liver Diseases especially non alcoholic fatty liver disease(NAFLD), non alcoholic steatohepapititis(NASH), with the increasing incidence of Diabesity-A Systematic Review.EC Endocrinology and Metabolic Research published in2020.

[7] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Mechanisms that associate extension of Nonalcoholic fatty liver diseases(NAFLD) to NASH (Nonalcoholic steatohepatitis) and further progressing to cirrhosis and Hepatocellular carcinoma(HCC) in addition to few proposed biomarkers for poor prognosis.J Gynaecol 2021;1(16):1-18.

[8] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How can we optimize therapy of Non Alcoholic Fatty Acid Liver Disease-A Short Communication on role of Astragaloside IV and other prospective agents". Clinical Research and Clinical Case Reports, 2021;1(3):1-4.
DOI: http;//doi.org/04.2021/1.1013.

[9] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Paradoxical Additional Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection-A Minireview". *Acta Scientific Gastrointestinal Disorders* 4.7 (2021): 15-26.

[10] Younossi ZM, Koenig AB,Abdelatif D,Fazel Y, Henry L,WymenM. Global epidemiology of non alcoholic fatty liver diseasemeta-analystic assessment of Prevalence, incidence andoutcomes. Hepatology 2016; 64:73-84.

[11] Angulo P,Kleiner DE,Dam-Larsen S,Adams LA,Bjornsson ES,Charat charoenwithalya P, etal. Liver fibrosis,but no other histological features ,is associated with long term outcomes of patients with Non Alcoholic Fatty Acid Liver Disease. Gastroenterology 2015; 149:389-97.

[12] Sayiner M, Koenig AB, Henry L, Younossi ZM. epidemiology of non alcoholic fatty liver diseaseand non alcoholic steatohepapititis in adults.Clin Liver Dis 2016; 20:205-14.

[13] GBD 2015.Mortality and causes of death Collaborators. Global,regional ,and national life expectancy ,all cause mortality,and cause specific mortality for 249 causes of death,1980-2015:a systematic review for the Global burden of disease study 2015.Lancet 2016; 388:1459--544.

[14] Younossi ZM, Stepanova M, Rafiq N,Makhlouf H, YounoszaiZ,Agrawal R,Goodman Z.Pathologic criteria for non alcoholic steatohepapititis :interprotocol agreement and ability to predict liver-related Mortality. Hepatology 2011; 53:1874-82.

[15] Konerman MA,Jones JC,Harrison SA. Pharmacotherapy for NASH:current and emerging: J Hepatol 2018;68: 362-75.

[16] Cusi K,Orsak B,BrilF,Lomonaco R,Hecht J,Ortiz-Lopez C , etal .Long term treatment for patients with non alcoholic steatohepatitis and pre Diabetes or type2 Diabetesmellitus: a randomized controlled trial.Ann Int Med 2016;165(5):305-15.

[17] Armstrong MJ,Gaunt P,Aithal GP,Barton D,Hull D,Parker R, etal .LEAN trial team .Liraglutidesafety and efficacy in for patients with non alcoholic steatohepatitis(LEAN):a multicenter ,double blinded, a randomized,placebo- controlled phase 2 study. Lancet 2016; 387:679--90.

[18] Caldwell S. NASH therapy:omega 3 supplementa-

tion, Vitamin E, insulin sensitizers and statin drugs. Clin Mol Hepatol 2017;23: 103-8.

[19] Abner EL,Schmitt FA,Mendiondi MS,Marcum JL,Kryscio RJ. Vitamin E and all cause Mortality:a meta-analysis.Curr Aging Sci 2011; 4:158-70.

[20] Schurks M,Glynn RJ,Rist PM,Tzurio C,Kurth T.Effects of Vitamin E on stroke subtypes: meta-analysis of randomized controlled trials.BMJ 2010; 341:C5702.

[21] Klein EA.Thompson IMJr,Tangen CM,Crowley JJ,Lucia MS, Goodman PJ, etal . Vitamin E and the risk of prostate cancer:the selenium and Vitamin E cancer prevention trial(SELECT).JAMA 2011; 306:1549-56.

[22] Sung KC,RyuS,LeeJY,Kim JY,Wild SH,Byrne CD.Effect of exercise on the development ofnew fatty liver and the resolution of existing fatty liver. J Hepatol 2016;65: 791-7.

[23] Chalasani N, Younossi ZM, Lavine AE,Charlton M, Cusi K, RinellaM, et al .The diagnosis and management of of non alcoholic fatty liver disease: practice guidance from the American Association for thestudy of Liver disease. Hepatol 2018;67: 328-57.

[24] Neuschwander –Tetri BA,Loomba R,Sanyal AJ,Lavine AE,Van Natta ML, RinellaM, Abdelmalek MF, et al. NASH Clinical Research Network. Farsenoid X nuclear receptor ligand Obeticholic acid for non cirrhotic, non alcoholic steatohepatitis(FLINT):a multicenter, randomized,placebo- controlledtrial . Lancet 2015; 385:956--65.

[25] Ratziu V,Harrison SA,Francque S,Bedossa P,Lahert P,Serfaty L, etal .GOLDEN 505 Investigator Study Group. Elafibranor,an agonist of the Peroxisome Proliferator Activated Receptor α,and δ induces resolution of non alcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016; 150:1147-59.

[26] Friedman SL, Ratziu V,Harrison SA, Abdelmalek MF, Aithal GP,Caballeria J, etal .A randomized,placebo- controlledtrial of cenicriviroc for the treatment of non alcoholic steatohepatitis with fibrosis. Hepatology 2018; 67:1754-67.

[27] Harrison SA,Bashir MR,Guy CD,Zhou R,Moylan CA,Frias JP, etal . Resmetriom(MGL-3196) for the treatment of non alcoholic steatohepatitis: multicenter ,double blinded, a randomized,placebo- controlled phase 2 trial. Lancet 2019; 394:2012--24.

[28] Ratziu V,Ladron-de-Guevara L,Safadi R,Poordad F,-Fuster F, Harrison SA, et al.The ARREST Investigator Study Group.One year results of the Global phase 2b randomized,placebo- controlled ARREST trial of aramchol,a stearoyl-Co A desaturase inhibitor,in patients with NASH . Hepatology 2018; 68:1447A-8A.

[29] Pelliciari R, Costantino G, Camioni E,Sadeghpour BM,Entrena A,Willson TM, etal . Bile acid derivatives as ligands of the Farsenoid X receptor:synthesis, evaluation and structure Activity relationship of a series of body and side chain modified analogues of chenodeoxycholic acid. J Med Chem 2004; 47:4559-69.

[30] Jhaveri MA,Kowdley KV.New developments in the treatment of primary biliary cholangitis:role of Obeticholic acid .Ther Clin Risk Manag 2017; 13:1053-860.

[31] Jeong SW. Non alcoholic fatty liver disease:A Drug revolution is coming . Diabetes Metab J 2020;44:640-57.

[32] Adorini L,Pruzanski M,Shapiro D. Farsenoid X receptor targeting to treat non alcoholic steatohepapititis ,Drug Discov Today 2012; 17:988-97.

[33] Pelliciari R,Fiorrucci S,Camioni E,Clerici C,Costantino G,Malony PR, etal .6Alpha-ethyl- chenodeoxycholic acid(6ECDCA),a potent and selective FXR agonist with anticholestatic activity.J Med Chem 2002; 45:3569-72.

[34] Mudaliar S,Henry RR,SanyalAJ,Morrow L,Marshall HU,Kipnes M, etal .Efficacy and safety of the Farsenoid X receptor agonist Obeticholic acid in patients withtype2 Diabetes mellitus and of non alcoholic fatty liver disease. Gastroenterology 2013; 145:574-82.

[35] Younossi ZM, Ratziu V, Loomba R,RinellaM, Anstee QM, Goodman SM, etal .REGENERATE 505 Investigator Study Group.Obeticholic acid for the treatment of non alcoholic steatohepatitis: interimanalysis from a multicenter ,double blinded , placebo- controlled phase 3 trial. Lancet 2019; 394:2184-96.

[36] Pockros PJ,Fuchs M,Freilich B,Schiff E,Kohli A, Lawitz EJ, et al. CONTROL :A a randomized, phase 2 study on Obeticholic acid and atorvastatin on lipoproteins in non alcoholic steatohepatitis.Liver Int 2019; 39:2082-93.

[37] Eaton JE,Vuppalachi R,Reddy R,Sathapathy S,Ali B,Kamath PS. Liver injury in patients with cholestatic Liver disease treated with Obeticholic acid. Hepatology 2020; 71:511-4.

[38] Tully DC,Rucker PV,Chianelli D,Williams J,Vidal A,Alper PB, etal .Discovery of Tropifexor(LIN-452),a highly potent non bile acid fxr agonist for the treatment of cholestatic Liver disease and non alcoholic steatohepatitis(NASH). J Med Chem 2017; 60:9960-73.

[39] Sanyal AJ,Lopez PM, Lawitz EJ, Kim W,Huang JF,Andreone P, etal . Tropifexor (TXR), an FXR agonist for the treatment of NASH: interim results from

DOI: https://doi.org/10.30564/jer.v3i2.3580

the first two parts of phase 2b study FLIGHT- FXR. Hepatology 2018; 68:1460A-1A.

[40] Sanyal AJ,Lopez PM, Lawitz EJ, Kim W,Huang JF,Andreone P, etal . Tropifexor, a Farsenoid X receptor agonist for the treatment of non alcoholic steatohepatitis: interim results based on baseline body mass index from the first two parts of phase 2b study . FLIGHT- FXR. J Hepatol 2019;70(ISuppl): E796-7.

[41] Trauner M,Gulamhusein A,Hameed B, Caldwell S,Shiffman ML,Landis C, etal . The nonsteroidal a Farsenoid X receptor agonist Cilofexor(GS-9674), improves markers of cholestasis and Liver injury in patients with primary sclerosing cholangitis. Hepatology 2019; 70:788-801.

[42] Lawitz EJ,Herring RJr, Younes ZH,Gane E,Ruane P,Schall RA, etal .Proof of concept studyof an apoptosis Signal regulating kinase(ASK1) inhibitor(selonosertib)in combination with an acetyl – CoA carboxylase inhibitor((GS-0976), or a Farsenoid X receptor agonist (GS-9674),in NASH. J Hepatol 2018;68(ISuppl): S57.

[43] Patel K, Harrison SA,Elkhashab M,Trotter JE, Herring R,Rojiter SE, et al. Cilofexor,A nonsteroidal a FXR agonist,in non cirrhotic patients with NASH :a phase 2 randomized controlled trial. Hepatology 2020; 72:58-71.

[44] Chianelli D ,Rucker PV,Roland J, Tully DC,Nelson J,Liu XC, etal. Nidufexor(LMB763),a novel FXR modulator for the treatment of non alcoholic steatohepatitis. J Med Chem 2020; 63:3868-80.

[45] Erstad DJ,Farrar CT,Ghoshal S.Masia R,Ferreira DS,Chen YJ, etal. Molecular magnetic resonance imagingaccurately measures the antifibrotic effect of EDP-305,a novel Farsenoid X receptor agonist. Hepatol Commun2018; 2:821-35.

[46] Ornitz DM,Itoh N.The Fibroblast growth factor signaling pathway. Wiley Interdiscip RevDev Biol2015; 4:215-66.

[47] Schaap FG,Trauner M,Jansen PL. Bile acid receptors as targets for drug development. Nat Rev Gastroenterol Hepatol 2014; 11:55-67.

[48] Harrison SA, RinellaME, Abdelmalek MF, Trotter JF,Paredes AH,Arnold HL, et al. NGM282 for treatment of non alcoholic steatohepatitis:a multicenter, randomized, double blinded, placebo- controlled phase 2 trial. Lancet 2018; 391:1174-85.

[49] Harrison SA,Rossi SJ, Paredes AH, Trotter JF, Bashir MR,Guy CD, et al. NGM282 improves Liver fibrosis and histology in 12weeks in patients with non alcoholic steatohepatitis. Hepatology 2020; 71:1198-212.

[50] Cyphert HA,GeX,Kohan AB,Salati LM,Zhang Y,Hillgartner FB. Activation of the Farsenoid X receptor induces Hepatic expression and secretion of Fibroblast growth factor 21. J Biol Chem 2012;287:25123-38.

[51] Kharitonenkov A,Larsen P.FGF21 reloaded:challenges of a rapidly growing field. Trends Endocrinol Metab 2011; 22:81-6.

[52] Sonoda J,Chen MZ,Baruch A. FGF21 receptor agonists:an emerging therapeutic class for obesity – related diseases. Horm Mol Biol Clin Invest 2017; 30:20170002.

[53] Sanyal AJ,Charles ED, Neuschwander –Tetri BA,Loomba R, Abdelmalek MF, Harrison SA, et al. Pegbelfermin(MBS-986036),a Pegylated Fibroblast growth factor 21 analogue in patients with non alcoholic steatohepatitis:a , randomized, double blinded, placebo- controlled phase 2a trial. Lancet 2019; 392:2705-17.

[54] Berger J,Moller DE.The mechanisms of action of PPARs. Annu Rev Med 2002;53: 409-35.

[55] Pawlak M,Lefebvre P,Staels B. Molecular mechanisms of PPARα action and its impact on lipid metabolism , inflammation and fibrosis in non alcoholic steatohepatitis. J Hepatol 2015;62: 720-33.

[56] Francque S,Veerijken A,Caron S,Prawitt J,Paumelle R,Derudas B, etal. PPARα gene expression correlates with the severityand histological treatment response in patients with non alcoholic steatohepatitis. J Hepatol 2015;63: 164-73.

[57] Bojic LA,Huff MW. Peroxisome Proliferator Activated Receptorδ:A multifaceted metabolic player.Curr Opin Lipiodol 2013;24: 171-7.

[58] Riserus U,Sprecher D,Johnson T,Olson E,Hirschberg S,Liu A, etal. Activation of Peroxisome Proliferator Activated Receptorδ (PPAR δ) promotes reversal of multiple metabolic abnormalities ,reduces Oxidative stress,and increases fatty acid oxidation in moderately obese men. Diabetes 2008;57: 332-9.

[59] Boubia M,Poupardin O,Barth M,Binet J,Peralba P,Mounier J, etal.Design ,synthesis and evaluationof a novel series of indole sulfonamide Peroxisome Proliferator Activated Receptor (PPAR)α/γ/δ triple Activators :discovery of Lanfibranor,a new antifibrotic Clinical candidate . J Med Chem 2018; 61:2246-65.

[60] American Diabetes Association.8. Pharmacologic approaches to glycaemic treatment: Standards of medical care in Diabetes-2018. Diabetes Care 2018; 41:S73-85.

[61] Eng C,Kramer CK,Zinman B,Retnakaran R. Glucagon like peptide 1 Receptor agonist and basal insulin combination treatment for the management of type2

 DOI: https://doi.org/10.30564/jer.v3i2.3580

Diabetes:a systematic review and meta-analysis. Lancet 2014; 384:2228-34.

[62] Eguchi Y,Kitajima Y,Hyogo H,Takahashi H,Kojima M,Ono M, etal.Japan Study Group for NAFLD(JSG-NAFLD),Pilot study of with Liraglutide effects in non alcoholic steatohepatitis and non alcoholic fatty liver disease with glucose intolerance in Japanese patients (LEAN-J). Hepatol Res 2015;45: 269-78.

[63] Armstrong MJ,Houlihan DD,Rowe JA,Clausen WH,El-brond B,Gough SC, etal. Safety and efficacy of Liraglutide in patients with type2 Diabetesand elevated liver enzymes:individual patients data meta-analysis of the LEAD program. Aliment Pharmacol Ther 2013;37: 234-42.

[64] Shimizu M, Suzuki K,Kato K,Jojima T,Iijima T,MurohisaT, etal. Evaluation of the effect of Dapagliflozin,a Sodium –glucose cotransporter 2inhibitor on hepatic steatosis and fibrosis using transient elastography in patients with type2 Diabetes and non alcoholic fatty liver disease. . Diabetes Obes Metab 2019;21:285-92.

[65] Soccio RE, Chen ER,Lazar MA. Thiazolidenediones and the promise of insulin sensitization in type2 Diabetes. Cell Metab 2014;20:573-91.

[66] Chen Z,Vigueira PA,Chambers KT,Hall AM,Mitra MS,QiN, etal. Insulin resistance and metabolic derangements in obese mice are ameliorated by a novel Peroxisome Proliferator Activated Receptor γ sparing thiazolidenedione. J Biol Chem 2012;287:23537-48.

[67] McCommis KS,Hodges WT,Brunt EM,Nalbantoglu I,McDonald WG, etal.Targeting the mitochondrial pyruvate carrier attenuates fibrosis in a mouse model of non alcoholic steatohepatitis. Hepatology 2017; 65:1543-56.

[68] Colca JR, McDonald WG,Carey GS,Cole SL, Holewa DD,Brightwell –Conrad AS, etal.Identification of a mitochondrial target of thiazolidenedione insulin sensitizers(mTOT):relationship to newly Identified mitochondrial pyruvate carrier proteins.PLoS One 2013;8:e61551.

[69] Colca JR, McDonald WG,Adams WJ.MS-DC-0602K,a metabolic modulator directed at the core pathology of non alcoholic steatohepatitis. Expert Opin Invest Drugs 2018; 27:631-6.

[70] Harrison SA, Alkhouri N, Davison BA, Sanyal AJ, Colca JR,Edwards C, etal. Insulin sensitizer MS-DC-0602K, in non alcoholic steatohepatitis: a , randomized, double blinded , placebo- controlled phase IIb Study. J Hepatol 2020;72: 613-26.

[71] Lefebvre P, Moyle G, Reshef R,Richman LP, Thompson M, HongF, et al. Antifibrotic effects of the dual CCR2/CCR5 antagonist in cenicriviroc in animal models of Liver and Kidney fibrosis. PLoS One 2016;11:e1158156.

[72] Friedman SL, Sanyal AJ, Goodman SM, Lefebvre E, Gottwald M,Fischer L, Ratziu V. Efficacy and safety study of cenicriviroc for treatment of non alcoholic steatohepatitis in adult subjects with Liver fibrosis:CENTAUR Phase 2b study design.Contemp Clin Trials2016; 47:356-65.

[73] Sinha RA, BruinstroopE, Singh BK, Yen PM. Non alcoholic fatty liver disease and hypercholesterolemia:role of thyroid hormones, metabolites, and agonists. Thyroid 2019;29: 1173-91.

[74] Bohinc BN, MichelottiG, Xie G, Pang H, SuzukiA, GuyCD, et al. Repair related activation of hedgehog signaling in stromal cells promotes intra hepatic hypo thyroidism. Endocrinology 2014; 155:4591-601.

[75] Loomba R, Neutel J, Mohseni R, Bernard D, Severance R, Dao M, et al. A novel Liver Receptor beta agonist, significantly reduces Liver fat with both low and high doses in patients withNon alcoholic fatty liver disease:a Phase 2 randomized, placebo- controlledtrial. J Hepatol 2019;70(1Suppl): E150-1.

[76] Lelkin –Frenkel A, Gonen A, Shaish A, Goldiner I, Lelkin –Gobbi D, Konikoff FM, et al. Fatty acids Bile acid conjugate inhibits hepatic stearoyl-Coenzyme A desaturase and is nonatherogenic. Arch Med Res 2010; 41:397-404.

[77] Abu-Elheiga L, Brinkley WR, Zhong L, Chirala SS, WoldegiorgisG, Wakil SJ. The sub cellular localization of acetyl-CoA Carboxylase 2. Proc Natl Acad Sci USA 2000;97:1444-9.

[78] Brooks SC3rd, Brooks JS, LeeWH, LeeMG, Kim SG. Therapeutic potential of dithiolethiones for hepatic diseases. Pharmacol Ther 2009;124:31-43.

[79] Winder WW, Hardie DG.AMP-activated protein kinase, a metabolic master switch:possible roles in type2 Diabetes. Am J Physiol 1999;277:E1-10.

[80] Kim W, KimBG, Lee JS, Lee CK, Yeon JE, ChangMS, et al. Randomized Clinical trial:the Efficacy and safety study ofoltipraz, a liver X Receptoralpha –inhibitory dithiolethione in in patients with Non alcoholic fatty liver disease. Aliment Pharmacol Ther 2017;45: 1073-83.

[81] Abu-Elheiga L, Jayakumar A, Baldini A, Chirala SS, WakilSJ. Human acetyl-CoA Carboxylase characterization, molecular cloning and evidence for two isoforms. Proc Natl Acad Sci USA 1995;92:4011-5.

[82] Harriman G, Greenwood J, Bhat S, Huang X, Wang R, Paul D, et al. Acetyl-CoA Carboxylase inhibition BY ND -630reduces hepatic steatosis, improves insulin

  DOI: https://doi.org/10.30564/jer.v3i2.3580

sensitivity, and modulatesdyslipidaemia in rats. Proc Natl Acad Sci USA 2016;113:E1796-805.

[83] Loomba R, Kayali Z, Nurredin M, Ruance P, La M, et al. GS-0976 reduces hepatic steatosis and fibrosis markers in patients withNon alcoholic fatty liver disease. Gastroenterology 2013; 155:1463-73.

[84] Barondes SH, CastronovoV, Cooper DN, Cummings RD, Drickamer K, Feizi T, et al. Galectins: a family of animal beta-galactoside binding lectins. Cell 1994;76:597-8.

[85] Yang RY, Hsu DK, Liu FT. Expression of Galectin-3-modulates T-Cell growth and apoptosis. Proc Natl Acad Sci USA 1996;93:6737-42.

[86] Sano H, Hsu DK, Yu L, Apgar JR, Kuwabara I, Yamanaka T, et al. Human Galectin-3 is a novel chemoattractant for monocyte and macrophages. J Immunol 2000;165:2156-64.

[87] Tellez-Sanz –R, Garcia-FuentesL, Vargas Berenguel A. Human Galectin-3 selective and high affinity inhibitors. Present state and future perspectives. Curr Med Chem 2013; 20:2979-90.

[88] Harrison SA, Marri SR, Chalasani N, Kohli R, Aronstein W, ThompsonGA, et al. Randomized Clinical Study: GRMD-02, a Galectin-3inhibitor, vs placebo in patients having non alcoholic steatohepatitis with advanced fibrosis. Aliment Pharmacol Ther 2016;44: 1183-98.

[89] Chalasani N, Abdelmalek MF, Garcia-Tsao G, Vuppalanchi R, Akhouri N, RinellaM, et al. Belamectin (GRMD-02) Study Investigators. Effects of Belamectin, an inhibitor of Galectin-3, in patients with non alcoholic steatohepatitis with cirrhosis and portal hypertension. Gastroenterology 2020; 158:1334-45.

[90] Pedrosa M, Seyedkazemi S,Francque S, Sanyal AJ, RinellaM, et al. A Randomized, double blinded, multicenter, Phase 2b, study to evaluate the safety and Efficacy of a combination of tropifexor and cenicrviroc in patients with non alcoholic steatohepatitis andliver fibrosis: study design of the TANDEM Trial. placebo- controlled phase 3 trial. Contemp Clin Trials2020; 88:105889.

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