Master Thesis

Sex and gender aspects of nutrition and their impact on the prevalence of non-alcoholic fatty liver disease (NAFLD) among pre- and postmenopausal women

Do female dietary patterns and food habits play a key role in the pathogenesis of NAFLD?

submitted by

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STATUTORY DECLARATION

I declare that I have developed and written the enclosed master thesis completely by myself, and have not used sources or means without declaration in the text. Any thoughts from others or literal quotations are clearly marked. The master thesis was not used in the same or in a similar version to achieve an academic grading or is being published elsewhere.

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Abbreviations

ALT	alanine-aminotransferase
AST	aspartate-aminotransferase
BMI	Body Mass Index
CHC	Coronary Heart Calcification
(hs)-CRP	(high sensitivity) C-Reactive Protein
DAG	Di-Acyl-Glycerol
DGE	German Society for Nutrition
EASD	European Association for the Study of Diabetes
EASL	European Association for the Study of Liver
EASO	European Association for the Study of Obesity
ELF	European Liver Fibrosis panel
EPIC	European Prospective Investigation into Cancer and Nutrition
FFA	Free Fatty Acids
FFQ	Food Frequeny Questionnaire
FLI	Fatty Liver Index
FNRS	Finnish Nutritional Risk Score

GGT	γ- glutamyl- transferase
HCC	Hepatocellular Carcinoma
HOMA-IR	Homeostasis Model Assessment - Insulinresistance
IHBS	Irrational Health Belief Score
IL-6	Interleukin 6
IL-8	Interleukin 8
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
PCOS	Polycystic Ovarian Syndrome
SHBG	sex hormone binding globuline
T2DM	Type 2 Diabetes
TAG	Tri-Acyl-Glycerol
TGL	Triglycerides
TNF-alpha	Tumornecrosisfactor alpha

For reasons of readability, the male form is used with personal names, however the female form is also always intended

Abstract in English

Introduction

The features of the metabolic syndrome don´t include non-alcoholic fatty liver disease, but it is necessary to recognize NAFLD despite its wide spectrum of liver disease as a cardiovascular risk factor. NAFLD is linked with 75% of chronic liver diseases and strongly associated with obesity and T2DM. 70% of individuals with T2DM are affected by NAFLD. The intention of this narrative review was to find reliable data to answer the question if genderspecific food patterns have an impact on the prevalence of NAFLD among pre- and postmenopausal women and if there are sex- and genderspecific differences of pathogenesis of NAFLD.

Methods

A literature research was conducted to illustrate an overview of the recent data with focus on female characteristics of disease.

Results

Discussing the etiology of NAFLD endocrine disorders are playing an important role, and sex and gender differences can be recognized.

Postmenopausal women and women with endocrine disturbances such as PCOS are at high risk of being affected by NAFLD. The endogeneous estrogens have a protective effect, and change of hormone levels during menopause and change of adipose tissue distribution are related to an increasing incidence of female NAFLD. There is no evidence that genderspecific dietary behavior, especially female food choices, play a key role in the pathophysiologic mechanism of NAFLD. Fructose consumption from industrialised products is supposed to be a promotor of NAFLD in correlation with total daily calorie intake of macronutrients. The data suggest a higher level of health literacy and food behavior among women of all age groups compared to the male subjects.

Conclusion

Health professionals are confronted with the challenge of an early diagnosis by using sensitive reliable non-invasive diagnostic tools, including screening algorithms for high risk persons and furthermore providing a genderspecific nutritional support as a central part of therapy and disease prevention.

Keywords: genderspecific dietary behavior, NAFLD among women, Fructose and NAFLD

Abstract in German

Einleitung

Die nichtalkoholische Fettlebererkrankung (NAFLD) ist bislang nicht in der Definition des Metabolischen Syndroms enthalten, obwohl sie neben dem heterogenen Spektrum der chronischen Lebererkrankung einen bedeutenden kardiovaskulären Risikofaktor darstellt. 75% der chronischen Lebererkrankungen beruhen auf einer NAFLD und gleichzeitig besteht eine Assoziation mit Adipositas und T2DM. Das Ziel dieser Arbeit ist die Bearbeitung der Fragestellung, ob geschlechtsspezifisches Ernährungsverhalten einen Einfluss auf die Prävalenz der NAFLD bei prä- und postmenopausalen Frauen ausübt, bzw. ob geschlechts- und genderspezifische Unterschiede in der Pathogenese der weiblichen nicht-alkoholischen Fettleber entscheidend sind.

Methodik

Eine Literaturrecherche mit unten angeführten Suchbegriffen wurde durchgeführt.

Ergebnisse

Endokrine Stoffwechselvorgänge mit geschlechtsspezifischen Unterschieden spielen in der Pathogenese der NAFLD eine wichtige Rolle.

Postmenopausale Frauen und Frauen mit hormonell bedingten Erkrankungen wie z.B.: PCOS haben ein erhöhtes Risiko für eine NAFLD. Die endogenen Östrogene haben einen protektiven Effekt, die Menopause mit den begleitenden Veränderungen im Hormonhaushalt ist assoziiert mit einer zunehmenden androgenen Fettgewebsverteilung und ist in weiterer Folge mit einer steigenden Inzidenz der „weiblichen Fettleber“ verbunden. Es gibt derzeit keine Evidenz, dass geschlechtsspezifische weibliche Ernährungsmuster eine Schlüsselrolle in der Pathogenese der NAFLD einnehmen. Frauen aller Altersgruppen wird im Vergleich zu Männern ingesamt ein höheres Maß an Gesundheitskompetenz und Ernährungsbewusstsein zugeschrieben.

Schlussfolgerung

Der Auftrag für das interdisziplinäre Betreuungskonzept ist die Möglichkeit einer frühzeitigen, nichtinvasiven Diagnostik der NAFLD mit adäquaten Screeningmethoden für Hochrisikopersonen und ernährungsmedizinisch gestützten Präventionsstrategien.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver diseases and is recognized as the hepatic manifestation of metabolic syndrome linked with insulin resistance and higher cardiovascular morbidity and mortality.

The spectrum of NAFLD includes simple steatosis to NASH (non-alcoholic steatohepatitis) and finally cirrhosis.

The aim of the first part of this literature review is to illustrate NAFLD as a systemic disease, which is often associated with features of the metabolic syndrome and correlated with an increased cardiovascular risk.

Furthermore the main factors of pathogenesis are described with focus on sex- and genderspecific features of disease. Endocrine aspects of the complex of liver disorder should be explained, particularly the role of insulin resistance as well as the role of estrogens in the procedure of pathogenesis of NAFLD among women.

The second part of the review examines gender aspects of food choices and a possible correlation between sex- and genderspecific dietary patterns and the prevalence of non-alcoholic fatty liver disease among women. It refers to the question if there is the need for an early genderspecific nutritional support and screening strategy.

2. Methods

An electronic literature research was conducted by using following terms:

"NAFLD and women", "prevalence and epidemiology of NAFLD", "gender nutrition patterns" and "fructose and NAFLD". Different databases (Pubmed, Google Scholar and Cochrane library) were searched for reliable data. A manual search of references cited in retrieved articles was also performed to identify studies not found in the database search. Articles featured in this review were identified and selected by title, date of publication, English or German language and their relevance to the hypothesis.

At least recently published data were added in January 2017.
At the beginning the period of literature search was determined from 2000-2016, for the definite selection of studies and reviews, concerning prevalence and epidemiology of NAFLD, the period was determined from 2014-2016.
Concerning nutrition surveys and studies there was no limit defined, because on the one hand in the field of nutrition and nutrition related diseases there are only a few prospective controlled trials, on the other hand the majority of nutrition trials have a retrospective design or are part of a cohort subgroup. Some of the selected surveys had a follow-up period over 15 years.
Essential primary sources, which were cited in the included systematic reviews, were also mentioned to achieve a sufficient overview about the relevant data.

Further sources were manually selected from the literature reference lists of different meta-analysis, published reviews and studies, based on their title and relevance.
In detail the literature research was started in June 2016 by using the key terms, which were listed above. No reliable data were found in the context of female dietary behavior and NAFLD, so the research was divided in several keyword groups and the review was constructed in two parts: The first part deals with prevalence and pathogenesis of non- alcoholic fatty liver disease with focus on the “female NAFLD” in correlation to the hormonal status. The main question to answer was if men and women are differently affected by NAFLD related to their age and comorbidity and if there was a significant change of incidence during the past years in correlation with growing obesity.
The second part of the review has the aim to connect both parts of the central question, whether female dietary patterns play a key role in the prevalence of NAFLD or not. A large amount of data could be achieved in the context of fructose and NAFLD, but much less could be selected regarding gender aspects of nutrition.
The next step was achieving data for the differences between male and female food behavior and then constructing the correlation between dietary behavior and its potential impact on pathogenesis of NAFLD.
In detail, searching by the keywords “pathogenesis of NAFLD” in Pubmed 5943 results were found, after restriction for 5 years, 3849 results, containing 893

reviews, 2 of them were double found, finally 9 were selected by their title and relevance. By using the terms “NAFLD and women” in Pubmed 599 results were found, 53 of these were reviews, two recommended articles, in summary nine were selected, one review was excluded because the full text was written in Hungarian language.

By using “epidemiology of NAFLD” and “prevalence of NAFLD” and restriction of the period with the last 5 years, 1346 results were found, including 316 reviews, after further limitation of the period to 2 years (2014-2016) 190 reviews were selected at baseline and they were further checked by their title and relevance. With term “prevalence of NAFLD” 2011 results were found, including 502 reviews, after restriction to the period 2014-2016 1313 results with 317 reviews were detected and they were assessed by title and relevance.

The literature search, using the keyterms “Fructose and NAFLD”, achieved 244 results, five of them were selected.

In summary 84 sources were selected and cited in the review. The majority of the literature references contains reviews and meta-analysis because in the context of the hypothesis referring to female dietary patterns and their influence on the prevalence of NAFLD there were no adequate prospective nutrition study trials detected.

3. NAFLD

3.1. Epidemiology of non-alocholic fatty liver disease with focus on sex- and genderspecific differences of prevalence

In Europe as well as in the US non-alcoholic fatty liver disease (NAFLD) has risen to the mainly cause of chronic liver diseases. The data of NHANES describe the increase of NAFLD as part of chronic liver diseases, from 47% to 75% in the years between 1988 and 2008 [1].

NAFLD is strongly linked with the components of the metabolic syndrome, and a rising prevalence of metabolic conditions such as obesity, T2DM and insulin resistance contribute to the disease development.

Blachier et al. demonstrated in a comprehensive review of about 260

epidemiological studies the progressive prevalence of NAFLD with 2-44 % in the European population, 42,6-69,5% of people with T2DM are affected by NAFLD. NAFLD can be defined as an endemic disease in Europe with a potential threat to public health, associated with overweight and obesity [2].

More than 50% of European adults are overweight or obese, the prevalence of NAFLD in obese children is estimated with 36-44% [2]. NAFLD is associated with an increased risk of overall mortality and cardiovascular disease related mortality [2].

The term NAFLD contains a spectrum of liver diseases, which are characterised by a higher hepatic fat storage and includes bland steatosis as well as non-alcoholic steatohepatitis and at least liver cirrhosis with high risk for hepatocellularcarcinom.

El Kader et al. published 2015 a review in which they described the strong connection between NAFLD and components of the metabolic syndrome.

90% of persons with NAFLD are affected by the metabolic syndrome and the prevalence of T2DM among these individuals is reported in 33 to 50% [3].

Furthermore there is an interesting aspect regarding factors that influence the pathogenesis and progression of NAFLD:

The prevalence of the chronic liver disease is increasing with age, is more often reported among men younger the age of fifty, but there are higher prevalence rates among women older than fifty years [3].

Ethnicity is an important feature for the prevalence of NAFLD. Among the Asian population data describe the prevalence between 5-40% [3].

In addition to these data, Hynwoo et al. reported a prevalence of NAFLD in Korea with 25-30% of the population [4].

Hashimoto et al. suggested in their overview about gender differences in prevalence and severity of NAFLD and NASH that at the age of thirty the prevalence of NAFLD among men was of about 27% compared to 7% among women [5].

At the age of sixty the prevalence of NAFLD among women rises to 23%, while the prevalence among male persons doesn`t change. Regarding the prevalence of NASH the male patients are younger in age, but more women than men over the

age of fifty years are affected by NASH [5].

Regarding US population-based studies Hispanics have the highest, and non-Hispanic Blacks have the lowest prevalence of NAFLD [6].

Williams et al. also report a significantly higher prevalence of NASH in Hispanics than Caucasians (19.4% *vs.* 9.7%, $p = 0.03$) without a direct comparison of demographic parameters such as BMI [6,7].

An interesting fact in the analysis of Younossi et al. is the association of „lean NAFLD“ with younger age, female sex, and a decreased likelihood of having insulin resistance and hypercholesterolemia [8].

NASH was independently associated with being Hispanic (OR 1.72; 95%CI: 1.28-2.33) and inversely associated with being African-American (OR 0.52; 95%CI: 0.34-0.78) [6,8].

The pathogenesis may depend on genetic disposition and mutations.

The data of the NHANES III study from 1988-1994, including 11613 persons, described the prevalence of NAFLD among 2185 participants (=18,77%), 307 persons were defined with NASH. The importance of NAFLD as one of the leading causes of liver disorder is also expressed by the fact, that in the year 2009 9,7% of the liver transplantations were caused by NAFLD, in comparison to the data of 2001 with 1,2% of the transplantations [8,9].

Fickert describes the prevalence of NAFLD among people with T2DM and / or obesity with 75% and designates NAFLD as the hepatic manifestation of the metabolic syndrome and no longer as a solitary liver disease [10].

There are similar histopathologic changes between NAFLD in its different stages and alcoholic injured liver disease, while the clinical symptoms are completely different [11].

A main point is the early diagnosis of NAFLD after exclusion other pathogenetic patterns or secondary causes of liver disease. Referring to the “EASL/EASD/EASO Guidelines” NAFLD is the most common liver disorder in Western countries with a prevalence of 17-46% among adults, and also affecting 7% of normalweight persons, with a majority of females [12].

3.2. Diagnosis and Definition

NAFLD is defined as a condition in which more than 5% of hepatocytes exhibit macroscopic steatosis by light microscopy in the absence of other aetiologies of liver diseases [8].

Yki-Järvinen et al. suggest that half of persons with T2DM have NAFLD despite normal range levels of alanine - aminotransferase (ALT) [13].

The diagnosis requires evidence of steatosis either by imaging or histology without a secondary cause of steatosis such as medication, viral hepatitis, increased alcohol consumption (less than 20g/day for women, less than 30g/day for men) and negative tests for autoimmune liver diseases. The imaging techniques, such as ultrasound and MR, cannot differ between steatosis and steatohepatitis.

The invasive way of diagnosis with liver biopsy declares the different degrees of liver damage with the proof of ballooning degeneration as a form of hepatocyte cell damage and the different fibrosis scale which is not required for the diagnosis of NASH but is a strong predictor of advanced liver disease [13].

The coincidence of NAFLD and the metabolic syndrome is based on common pathophysiologic mechanisms. Both diseases entities are linked to higher cardiovascular risk and higher risk of developing hepatocellularcarcinom, combined with obesity and T2DM.

Turati et al. describe the positive correlation between T2DM and obesity as components of metabolic syndrome and the risk for hepatocellularcarcinom (HCC) by OR of 4,33 and 1,97 (95% CI) [14].

A subanalysis of the Edinburgh T2DM study 2011 expressed the prevalence of hepatic steatosis and NAFLD among 939 study participants with T2DM. Hepatic steatosis was found among 56,9% of the study population. Using the definition criteria and after excluding secondary causes, the prevalence of NAFLD was described among 42,6% of the study members [12].

On the other hand there already exist a few data which describe a higher risk of HCC in non-cirrhotic NAFLD which expresses the need for early screening of high risk patients [14].

NAFLD with or without steatohepatitis can predispose to HCC in the absence of cirrhosis or advanced fibrosis. Regarding the correlation between the components

of the metabolic syndrome and NAFLD, there is evidence for certain heterogeneity in NAFLD with a genetic predisposition. A gene variant in allele PNPLA3 is conferred to an increased risk of steatosis, NASH, fibrosis and cirrhosis and at least HCC, but without a higher risk of T2DM or higher cardiovascular risk.

Furthermore there must be looked at the non-invasive methods to determine the different stages of non-alcoholic fatty liver disease and their sensitivity and specificity to detect hepatic fibrosis.

Referring to the recently published EASL-EASD-EASO "Clinical Practice Guidelines for the management of the non-alcoholic fatty liver disease" NAFLD is characterised by excessive hepatic fat accumulation, in most cases associated with insulin resistance and defined by the presence of steatosis in more than 5% of hepatocytes, according to histological analysis or by a proton density fat fraction or quantitative fat/water selective magnetic resonance imaging "[15].

The term NAFLD contains two conditions of liver disease: non-alcoholic fatty liver and the non-alcoholic steatohepatitis. For the exact diagnosis other secondary causes for liver disease must be excluded, primarily a higher amount of daily alcohol consumption of about 20 g/day for women and more than 30 g/day for men.

The guidelines recommend the sonography as the first diagnostic step (A1), if the imaging procedure is not available, serum biomarkers and scores can be used alternatively. H-MRS can achieve a quantitative measurement of liver fat, but is not recommended for the clinical practice [15]

The second point is the surveillance of fibrosis progression of NAFLD. This can rely on a combination of biomarkers and transient elastography, but to define advanced fibrosis or cirrhosis the liver biopsy is the most accurate option [15]

Stefan et al. suggested that 70% of persons with NAFLD have normal levels of ALT and AST. On the other hand imaging with sonography is limited by its sensitivity, it can detect steatosis when liver content exceeds 33% [16].

3.3. Pathogenesis and pathophysiology

3.3.1. Lipidmetabolism

Byrne et al. described NAFLD as a multisystem disease, which leads to several extra-hepatic complications. The incidence rates of NAFLD are reported with 20/10000 person-years with a peak in the sixth decade, but referring to the difficulties of diagnostic procedures, the incidence data might be unprecise [17,18].

In accordance to the data of Blachier et al., which were mentioned at the beginning, the prevalence of NAFLD among persons with T2DM is indicated with 70% [2,17].

“NAFLD is an example of ectopic fat accumulation” and it is associated with a disorder of hepatokines and hormones controlling the glucose metabolism, especially increasing of gluconeogenesis and inhibition of insulin effects [19]. Furthermore the hepatic lipid storage causes insulin resistance and chronic inflammation with a progression of liver damage and fibrosis [19].

Byrne et al. described the association between adipose tissue distribution, fat accumulation in liver and the pathway of insulin resistance and attributed adipose tissue a key role in the pathogenesis of NAFLD [19].

The fat overflow from the adipose tissue increases the amount of long chain fatty acyl co-enzyme A in the liver, additionally increased by physical inactivity.

Fatty acyl Co-enzyme A are esterified with glycerol-3-phosphate to form monoacylglycerol, diacylglycerol (DAG) and triacylglycerol (TAG) [19].

Long chain fatty acids are used for the synthesis of ceramides and leads furthermore to the direct activation of protein phosphatase-2 with decreasing insulin signalling. Fatty acids, which are not used in oxidative metabolism are used in lipogenesis, increasing synthesis of intermediate lipid products such as DAG, TAG and di-palmitoyl phosphatidic acid enhances insulin resistance.

Diacylglycerol (DAG) can be hydrolysed to glycerol by releasing fatty acids, glycerol can be used as a substrate for gluconeogenesis, the synthesis of DAG is known as an important cause for hepatic insulin resistance, the conversion of TAG to DAG is controlled by TAG lipase. Gene identification-58 is an activator of adipose TAG lipase, in the next step DAG activates protein kinase C membrane

translocation to decrease the insulin pathway [19].

The synthesis of DAG is connected with inflammatory pathways and may contribute to hepatic production of inflammatory cytokines. There is evidence that intestinal microbiota and changes in diet may also affect several hepatic lipid pathways and may increase hepatic inflammation and fibrosis [19].

The illustration below describes the aspects of hepatocyte damage and its association with changes of lipid metabolism in the pathogenesis of NAFLD.

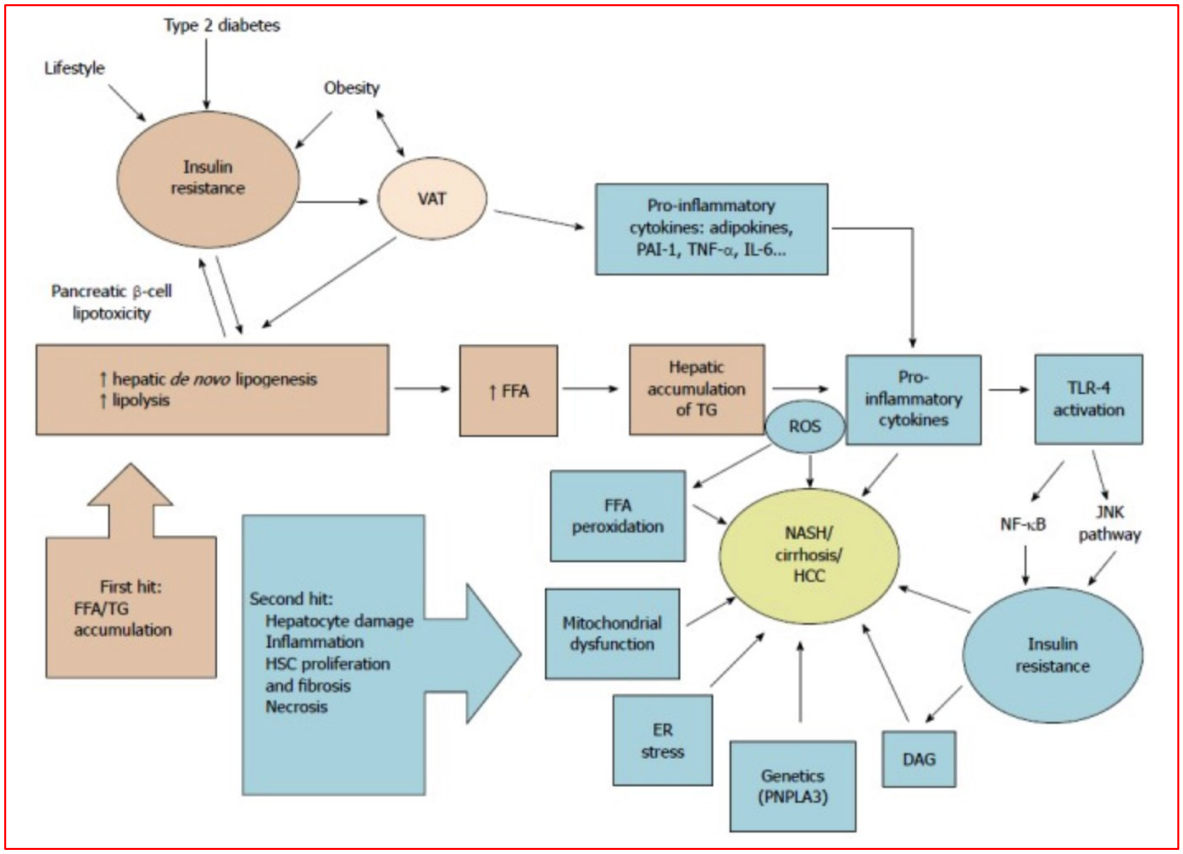

Figure 2: Pathophysiology of NAFLD, adapted from Marino, L. & Jornayvaz, F.R., 2015. Endocrine causes of nonalcoholic fatty liver disease. World Journal of Gastroenterology, 21(39), pp.11053–11076.

Byrne et al. referred in their review to the NHANES III survey findings, which suggest an association of NAFLD with an increased prevalence of cardiovascular diseases and a 70% increased risk of all cause mortality, while the cardiovascular events obtained a leading position. There is evidence for NAFLD as a multisystem disease. The prevalence of chronic kidney disease among persons with NAFLD is described with a range from 20-55% compared to 5-35% in persons without

NAFLD [17,20]. Proinflammatory cytokines from the adipose tissue are discussed as a pathophysiologic link [17,20].
Furthermore there is evidence to assume that patients with NAFLD have changes in myocardial substrate metabolism, especially myocardial insulin resistance, which may be linked with an increased risk of congestive heart failure [17].

3.3.2. Endocrine aspects of disease and adipose tissue

The term non-alcoholic steatohepatitis was first mentioned by Ludwig in 1980 during observations of patients with histological sign of alcoholic hepatitis without a history of alcohol consumption.
Most of the patients were obese women, the term NAFLD was introduced 1986 to describe a spectrum of liver diseases covering from hepatic steatosis to fibrosis and cirrhosis [21].
It is well known that NAFLD has a strong association with T2DM. The pathway of insulin resistance plays a key role in the disease development [21].
Visceral fat distribution enhances insulin resistance by accumulation of free fatty acids in the liver. Marino et al. described in their review the different adipokines, which are produced by adipose tissue and are involved in lipid metabolism [21]:

Leptin
Leptin is secreted mainly by adipocytes, further by skeletal muscle, stomach liver and ovaries and it is an anorexigenic, antilipogenic hormone to decrease appetite and insulin secretion. Insulin resistance is associated with high leptin levels, additionally, elevated leptin levels are correlated with NASH and fibrosis severity and they can be adjusted by age, BMI and gender [21].
Adiponectin
Adiponectin is an anti-inflammatory cytokine, secreted by adipocytes in an inverse correlation to visceral fat content. Low adiponectin levels are associated with diabetes and insulin resistance as well as NAFLD and dyslipidemia.
Adiponectin can decrease the production of free fatty acids in the liver and is correlated with progression of NAFLD [21].
The question arises if there are sex-specific differences in the pathway of the

different adipokines.

The differences of secretion of adipocytokines and adipose tissue distribution also play a role in the pathogenesis of NAFLD among young adults [21].

Ayonride et al. described the correlation of genderspecific adipose tissue distribution and the prevalence of NAFLD in an examination of a subpopulation of the RAIN cohort (prospective cohort of pregnancy, childhood and adolescence), which contained 83% of the primary study group (=1771 persons) with a mean age of 17 years [22].

The data suggest that the prevalence of NAFLD was higher among female participants than among male (16,3% vs. 10,1%, p= 0,004) while the fibrosis range was higher among the male subjects (3,1% vs. 2,2%).

The prevalence of NAFLD among obese males compared to females was 65% vs. 57% [22].

Waist circumference was used as parameter for central obesity, the findings demonstrated that more females than males had central obesity (33,2% vs. 9,9%) and the genderspecific adipose distribution also differs:

Females had greater mean subcutaneous adipose tissue than males, the subcutaneous to visceral adipose tissue ratio was higher in women than man.

In summary, waist circumference reflected subcutaneous adiposity more exactly than visceral adiposity. Surprisingly, the prevalence of NAFLD was higher among females than males (16,3 vs. 10,1; p= 0,004) in contrast to the results of other studies, which suggest a higher prevalence among males. A possible explanation for this fact can be the number of female adolescents with central obesity and normal range of ALT levels [22].

Elevated liver enzymes were no inclusion criteria for the cohort study to avoid a gender bias because of the fact that men generally have higher ALT levels than women.

To describe gender aspects of NAFLD, it is important to recognize that male NAFLD is generally associated with higher levels of ALT, a greater risk of metabolic syndrome, higher adiponectin and lower leptin levels than women and at least, greater visceral adipose tissue thickness, but similar insulin resistance.

The results of the adolescent study describe interactions between sex hormones, adipose tissue distribution and adipokines to explain gender differences of the

pathogenesis of NAFLD.
Females had a higher prevalence of NAFLD, but fewer metabolic risk factors than male adolescents [22].
Subucutaneous adipozytes produce higher levels of leptin and a higher number of estrogen receptors. With growing age and weight gain, especially after menopause, viscerally adipose tissue is becoming more dominant [23,24,25].
Another importing point was the role of subcutaneous adipose tissue as an independent predictor for NAFLD among adolescents, but 90% of abdominal fat of children is subcutaneous adipose tissue. Skinfold thickness was shown to be a more sensitive parameter for adolescent obesity than BMI [22].

3.3.3. Influence of estrogens - sex and gender aspects of disease

Polycystic ovary syndrome (PCOS) is an endocrine disorder of women in childbearing age with a prevalence of 8-15%, which is characterised by hyperandrogenism, oligo-/amenorrhea and polycystic ovarian morphology. Different genes influencing obesity, insulin resistance, betacell-dysfunction and steroid metabolism play a role in the pathogenesis of PCOS. Data show a prevalence of insulin resistance among women with PCOS with 50%.
The coincidence of NAFLD and PCOS is reported with 15 to 55%, whereas the prevalence of PCOS among women with NAFLD is reported by 71% in one cohort study [21].
Cerda et al. published similar data of prevalence, in their prospective trial 41 premenopausal women with PCOS were compared to 31 premenopausal women without PCOS, matched by age and BMI [26].
41,5% of the PCOS group achieved the sonographic diagnosis of hepatic steatosis compared to 19,4% of the control group. ALT levels were higher among the females with PCOS compared to the subjects of the control group (27,83+/- 20,66 vs. 15,5+/- 20,02; p= 0,018), but in summary 50% of the PCOS group had an elevation of ALT [26].
Insulin resistance enhances hyperandrogenism and decreases the secretion of sex hormone binding-globuline (SHBG), which inversely promotes insulin resistance.

Adiponectin levels and estrogen levels are lower among women with PCOS, hyperandrogenism is linked with higher ALT levels.

There is evidence that estrogens are a protective agent in the pathogenesis of NAFLD. NAFLD has a higher prevalence in postmenopausal than in premenopausal women [21].

Estrogens regulate growth hormone production and energy and lipid homeostasis, the replacement of estrogens among patients with estrogen deficiency leads to improvement of insulin resistance and regression of steatohepatitis [21].

Testosterone plays a central role in insulin sensitivity and lipid metabolism. Low levels of testosterone and SHBG are predictors of the metabolic syndrome, and are linked with higher visceral adipose tissue accumulation [21].

Durazzo et al. illustrated an overview of gender aspects of liver diseases, and referring to non-alcoholic fatty liver diseases, they summarized that the female distribution of adipose tissue is crucial for the fact, that women need a higher range of obesity to achieve the same metabolic disorder as men. Visceral adiposity is connected with postmenopausal age [27].

Data suggest that endogenous estrogens have a protective effect in the pathogenesis of NAFLD, which may explain the rising prevalence among postmenopausal women.

Völzke et al. pointed out the correlation of postmenopausal status and NAFLD referring to the changes of fat distribution during the hormonal changes during the menopausal period [28].

The question arises if we must treat non-alcoholic liver disease as a mainly endocrine disorder.

The influence of estrogens and insulin resistance in the process of pathogenesis of NAFLD can be recognized among women with PCOS.

The pathophysiologic mechanisms, which are promoted by endocrine disorders, are shown in the figure below: Insulin resistance, estrogen deficiency and hyperandrogenism are strongly linked with the increases hepatic de novo lipogenesis.

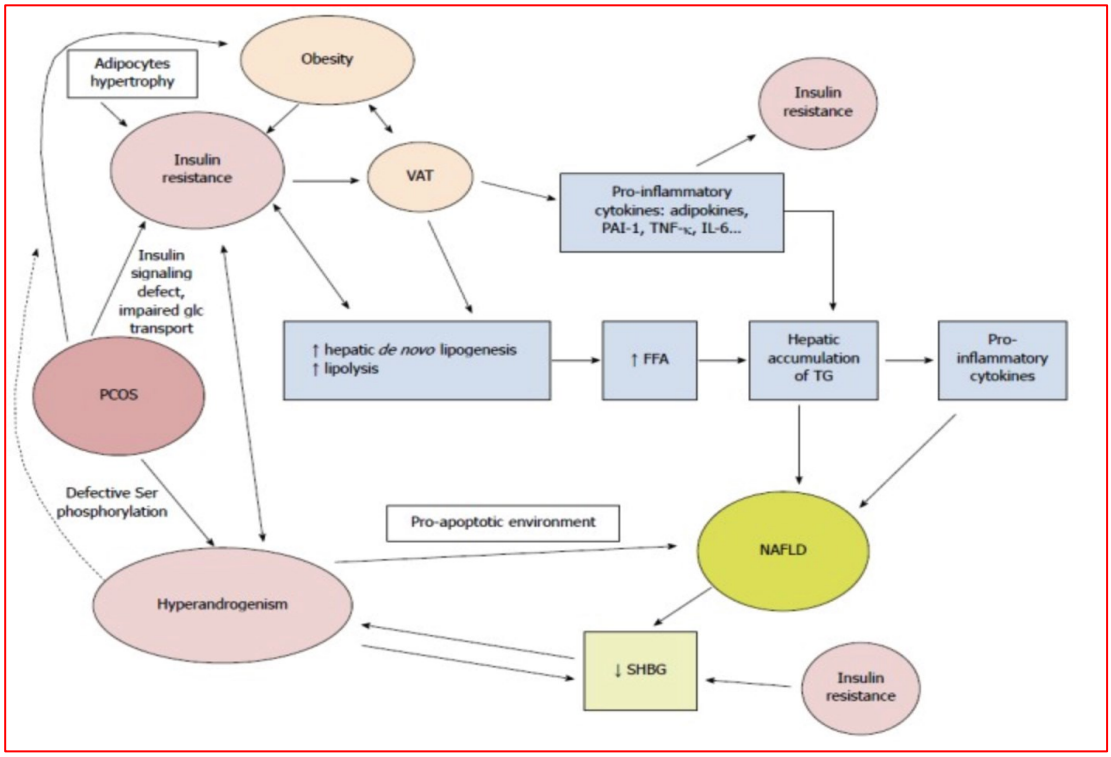

Figure 1: Pathophysiologic link between PCOS and NAFLD. adapted from Marino, L. & Jornayvaz, F.R., 2015. Endocrine causes of nonalcoholic fatty liver disease. World Journal of Gastroenterology, 21(39), pp.11053–11076.

Ramezani-Binaby et al. included seven studies in their meta-analysis to describe the prevalence of NAFLD among women with PCOS comparing to a healthy control group. Their findings showed a 3,93 fold increase in the risk of NAFLD for women with PCOS with enormous ethnic differences of prevalence [29].
NAFLD was diagnosed among 73,3 % of Brazilian women with PCOS comparing to 55% of the American women and 32% among Chinese women with 32,9% [29].

Angulo et al. recognized in their investigations that the prevalence of NAFLD among US adults differ in relation to their ethnicity: 45% of Hispanic adults are affected, compared to 33% of white people and 24% of blacks. These data are consistent to the findings of Williams et al., which were announced earlier in the chapter 3.1. [30,6]. In addition to endocrine disorder the differences can rely on different food habits, life style and intensity of exercise.

The second point in the meta-analysis was the correlation between obesity and the co-incidence of NAFLD and PCOS. Obese women with PCOS undergo a higher risk of NAFLD compared to normalweight women with PCOS [29].
The interaction of estrogens in the process of hepatic fibrogenesis and their impact on the severity of fibrogenesis were the main point of a cross-sectional study of Ju Dong Yang et al. in the year 2015 [31].
541 patients with histological diagnosis of NASH were randomized, the females were divided into premenopausal and postmenopausal women compared to the male group. The sex and menopause classification was the main predictor, other variables such as hypertension and diabetes, BMI were recognized as possible confounders.
The histological graduation of fibrosis showed a higher grade of severity among male and postmenopausal female participants with a 60-70% increased risk compared to the group of premenopausal women. At the age of 50 years the risk of advanced fibrosis was increasing among women, but not among the male group [31].
The potential protective effect of estrogen replacement therapy on fibrosis severity among postmenopausal women with NASH was supposed to be correlated with a risk reduction, but there was no statistical significance. Ju Dong Yang et al. referred in their trial to the data of the NHANES Study, which suggest a lower risk of NAFLD in postmenopausal women who are taking hormone replacement therapy than those who don´t have an estrogen medication [31].
The limitations of these trials are the high number of confounders, which must be taken into consideration.

3.3.4. Correlation with the metabolic syndrome - Precursor or cause?

At the beginning of the article non-alcoholic fatty liver disease was announced as the hepatic manifestation of the metabolic syndrome.
By answering the question of pathogenesis and progression, non-alcoholic fatty liver disease must be discussed as a heterogeneous liver disorder and there are data, which request that NAFLD precedes the metabolic syndrome and that it is a

strong determinant for the development of the features of metabolic syndrome.
The recent definition of metabolic syndrome doesn't include hepatic steatosis, despite its proven association, it is a complex of cardio-metabolic conditions, such as dyslipidemia, high blood pressure, waist circumference / overweight and impaired glucose metabolism. A central determinant is the visceral adipose tissue storage and distribution, which regulates the fat flow between intestine and liver and cholesterol synthesis [32].
Impaired glucose tolerance and diabetes, hypertension and dyslipidemia are linked to visceral adipose tissue with or without adiposity. It is important to recognize that free fatty acids and triglycerides decrease glucose utilisation because of the intensified oxidation. Furthermore they reinforce the insulin resistance of the muscle and by that way, increasing insulin requirement and increasing the risk of T2DM [32].

Conclusively the metabolic syndrome is a pathophysiologic concept with various risk factors, which are strictly linked to each other and lead to a markedly increased cardiovascular risk.
Lonardo et al. constructed a systematic review to confirm the paradigm of NAFLD as a precursor of the metabolic syndrome.
One of the main results was the fact, that NASH is more closely associated with T2DM than benign hepatic steatosis, but NAFLD as well as NASH are linked with a higher risk for developing T2DM [33].

The key role of insulin resistance is summarized by following statement: „Insulin resistance undoubtedly plays a major role in the pathophysiology of the metabolic syndrome". Insulin resistance is defined as the critical connector linking stress, visceral adiposity, and decreased cardio-respiratory fitness with increased cardiovascular disease" [33]. Hepatic insulin resistance is defined by elevated fasting glucose, whereas peripheral insulin resistance is characterised by high free fatty acids (FFA) concentrations [33].

3.3.5. NAFLD and cardiovascular risk

Referring to the introduction, NAFLD and its wide spectrum of disease severity is named as the hepatic manifestation of the metabolic syndrome, a fact that implicates an increased cardiovascular risk.
Data suggest NAFLD as an independent cardiovascular risk factor, but which pathophysiologic mechanisms define NAFLD as an atherogenic condition?

Hong Liu et al. demonstrated in their review the prevalence of cardiovascular diseases among individuals with NAFLD [34]. NAFLD is associated with earlier endothelial dysfunction in patients with arteriosclerosis compared to the control group, the prevalence of atrial fibrillation is higher among persons with NAFLD [34,35].
The elevation of ALT is a surrogate parameter for coronary heart diseases among male persons, but not among female persons, which can implicate, that female NAFLD doesn't mean an elevation of ALT [34,36].
NAFLD is strongly connected with the components of the metabolic syndrome, especially T2DM and dyslipidemia, which may explain the coincidence of cardiovascular diseases [34].
On the other hand there exist data that oxidative stress and inflammation are the triggers for the development of NAFLD combined with the production of pro-inflammatory cytokines such as TNF-alpha, IL-6, CRP and IL-8.
This implicates an atherogenic circumstance and can be the link between NAFLD and cardiovascular diseases, defining NAFLD as an independent cardiovascular risk factor [34].
Franque et al. showed in their review the association of increase IL-6 levels in presence of histologically diagnosed NASH, similarly levels of hs-CRP were elevated in combination with hepatic steatosis [37].
Fetuin A is a hepatokine, which is associated with insulin resistance and is highly expressed in the presence of NAFLD. It causes the expression of inflammatory adipokines, but inhibits the expression of adiponectin [37].
Physiologically, women have higher adiponectin levels than men and there is supposed to be a negative correlation of adiponectin and cardiovascular diseases,

but at the moment there are no reliable data to claim adiponectin as a surrogate parameter [38].
The prevalence of NAFLD among women increases with postmenopausal status, but what are further specific risk factors for female NAFLD?

Goh Eun Chung et al. conducted a cohort study with 1423 female persons, the findings show a strong correlation between central obesity and insulin resistance and NAFLD among pre- and postmenopausal women. The prevalence of NAFLD was reported with 20,7%, compared to the results of Hashimoto et al. with 27%, while the prevalence was higher among the postmenopausal women [39].
The combination of estrogen deficiency and relative androgen excess may lead to change of body fat composition and increase of visceral fat and by this way rising insulin resistance.
Clinical trials didn't show a benefit for women with hormone replacement therapy [39,40,41].
In the present literature research only one trial (Yang et al.) describes a probably positive effect of hormone replacement, it was already mentioned in the first part.
Regarding these data postmenopausal women with clinical or subclinical diagnosis of NAFLD seem to be at specific high cardiovascular risk.
It is well known that cardiovascular diseases are the leading cause of mortality in postmenopausal women, the findings of Min Kyung Kim et al. describe the correlation of NAFLD and coronary artery calcification among women at this life period [42].
919 postmenopausal women were included in the retrospective analysis. NAFLD was diagnosed by ultrasonography and coronary artery calcification was examined by a multi-detector scanner, additionally to weight, height and BMI [42].
The prevalence of NAFLD was evaluated with 31,9% among women, the prevalence of coronary heart calcification was determined among 19,7% of the female persons.
There was a significant association of CHC and NAFLD after considering other cardiovascular risk factors (BMI, age, hypertension, lipid parameters), and a strong link between insulin sensitivity, defined by HOMA-IR and severity of fatty liver disease [42].

Furthermore the prevalence of NAFLD among the premenopausal women, who participated in the analysis (748 persons) was determined with 19,7% compared to the data of Hashimoto et al. who defined the prevalence less than 10%.
Following the results of Min Kyung Kim insulin sensitivity and insulin resistance are a strong link between NAFLD and coronary artery calcification [42].
Furthermore the findings of the MESA cohort study reported the correlation between NAFLD and cardiovascular risk and demonstrated the link to systemic inflammation. MESA (Multiethnic study of arteriosclerosis) was an observational cohort study, which includes 8614 male and female participants at the age of 45-84 years with different ethnicity, the final population included 3976 persons.
Participants with NAFLD had higher prevalence of CRP levels >2 mg/lL (OR=2,22, 95% CI 1,85-2,67). 63% of the study members with NAFLD and 46% of the persons without NAFLD had hsCRP levels ≥2 mg/lL. The prevalence of subclinial arteriosclerosis was higher among the individuals with NAFLD than among those without NAFLD (54% vs. 50%) [43].
An interesting aspect is that a stronger correlation existed among women with NAFLD and increased inflammation after adjusting for age, ethnicity, smoking status and lipid parameters [43].

3.3.6. Influence of nutrition on pathogenesis

As we know nutrition and food patterns play a role in the pathogenesis of various diseases, there are a lot of data, which define nutrition as an important component in the process of liver disorder.
In the following part a short overview of the recent data is illustrated.
First of all an excessive intake of calories combined with a lack of physical activity can lead to intrahepatic fat accumulation and hepatotoxicity, in addition to different genetic susceptibility which explains the fact, that there are healthy obese individuals on the one hand and normalweight individuals with “lean NAFLD” on the other hand [44].
In the discussion about dietary behavior and the development of NAFLD, there is evidence that a high fat diet leads to an intense free fatty acids supply to the liver

as well as that individuals with NAFLD have typical dietary patterns characterised by a higher consumption of saturated fats and cholesterol and lower amount of fibres, antioxidants and polyunsaturated fats [45].

There are reliable data indicating, that daily fructose consumption is higher among persons with NAFLD compared to healthy individuals [45,79].

A high fructose diet decreases the hepatic lipid oxidation and leads to endoplasmatic reticulum stress in the liver by activating several proteinkinases and well augmented liver fat deposition and chronic inflammation [45].

Fructose consumption has risen over the past decades because fructose is contained in sweetened beverages, soft drinks and commercial products containing high fructose corn syrup. Main sources of dietary fructose are sucrose and high fructose corn syrup.

Mc Carthy et al. summarized in their review the role of fructose in metabolic disorders with the fact that increased fructose consumption is associated with the rising prevalence of NAFLD, obesity and diabetes and an increase of liver enzymes [46].

Data suggest that a high-fructose diet decreases hepatic insulin sensitivity, may influence the central nervous system and supports increased energy consumption and weight gain [46,47,48,49].

On the other hand Mei Chung et al. conducted a comprehensive systematic review to examine the effect of fructose, sucrose and high fructose corn syrup on liver health and suggest after looking at 21 intervention studies and six observational studies, that there is little evidence to declare the association of fructose consumption and liver disorder [50].

However this controversial statement can be explained by the amount of heterogeneous data as well as high risk of bias and inconsistent study findings because there are a few trials which provide data about fructose consumption and its correlation with NAFLD compared to glucose consumption, and data about the complex of increases of body weight and energy intake and their influence on progression of liver fat [50].

Only one double-blind study differentiated between possible effects of high fructose and glucose diets on liver lipid storage and biochemistry [51].

32 healthy overweight male individual received either a high-fructose or a high-glucose diet (= 25% energy), hepatic levels of triacylglycerol (TAG) and adenosine triphosphate as well as TAG levels in serum, insulin resistance and transaminases were measured. High-fructose and high-glucose diets were associated with changes in hepatic concentration of TAG and serum levels of liver enzymes without any significant difference. These findings suggest that excessive energy intake plays a more important role for liver health than the biochemical structure of carbohydrates.

Summarizing the work of Johnston et al., there exists a few evidence, that high fructose diet may increase liver enzymes and liver fat in healthy men compared to a balanced diet [51].

It is well known that the elevation of liver enzymes does not represent the range of liver disease or liver damage, which would enhance the need for invasive diagnostics such as liver biopsy to achieve an exact disease definition [52,53]. This conclusion is conform with the data of Chiu et al. and their study about the effects of fructose on the markers of NAFLD [54].

One further limitation of the review is that there is no statement, whether sex modifies the association of fructose consumption and liver disease or not.

The question arises if there are definitive differences of dietary behavior between men and women concerning fructose consumption. In the second part of the review sex and gender associated food habits will be discussed.

If we look back once more in medical history Yudkin et al. recognized an association between sugar consumption and coronary heart diseases [55,56].

Sucrose is a disaccharide, which contains one glucose molecule and a fructose molecule. Fructose is a hexose molecule and major component of fruits and honey.

Today the increase of industrialised food and sweetened beverages leads to the replacement of sugar by high fructose corn syrup, which has the advantage of a cheaper production and price. The rising consumption of sweetened beverages is mainly responsible for weight gain and increasing prevalence of diabetes and coronary heart diseases [55].

In former days fructose was mainly added in diabetic foods because fructose

consumption doesn't alter the insulin pathway and causes a fewer glycemia.
Nowadays the metabolic side effects of fructose are better known such as rising of plasma triglyceride, rising blood pressure and hepatic steatosis and rising serum uric acid [55]. The influence on lipid metabolism such as increase of plasma triglycerides by fructose consumption is lower among women compared to men, it is supposed that female sex hormones have a protective effect [55,57,58].
Recent data emphasize that a fructose intake over 50 g per day is associated with rising plasma triglyceride levels [55,59].
High fructose corn syrup in soft drinks and carbohydrate-sweetened beverages is a composition of 55% fructose, 41% glucose and 4% complex polysaccharides [60]. The increased consumption of fructose-enriched food is linked with increased prevalence of obesity, diabetes and non-alcoholic fatty liver disease in the US.
Fructose may prevent suppression of ghrelin which leads to impaired satiety and it can cause liver stress by activation of specific protein kinases and further reduction of hepatic insulin pathway [60].
M. Vos et al. summarized in their review that individuals with NAFLD have higher TGL levels after fructose intake than healthy individuals without NAFLD [61].
Vos et al. additionally presented data, which show that there is no difference if there is a supply with free fructose or sucrose because they seem to have similar health effects [61,62]. The main essence of the review is the summary of a pediatric study, which demonstrated a positive association between an increased carbohydrate intake of children and NAFLD.
There are only a few small case control studies with adults about fructose /soft drink consumption among individuals with NAFLD. But although there is still no strong evidence a high amount of fructose intake may be a trigger factor in the development of metabolic disorder, especially overweight and NAFLD.

4. Sex and gender aspects of nutrition

4.1. Comparison of female and male food choices - What is the evidence?

Do exist sex- and genderspecific dietary patterns and food behavior and does

nutrition play a key role in the development of liver diseases, especially female NAFLD?

4.1.1. FoodNET (Foodborne Diseases Active Surveillance Network

The population survey, which was launched in May 2006 through April 2007 in the context of the Foodborne Diseases Active Surveillance Network (FoodNet) included 14878 persons over 18 years, 38% of the participants were male persons, 62% of them were female persons [63].

FoodNet is a collaboration between the Center for Disease Control and Prevention`s Emerging Infections Program, Public Health Departments in ten US states, the Food and Drug Administration and the US Department of Agricultures Food Safety and Inspection Service.

The differences of food patterns were examined by telephone questionnaires after randomized selecting procedure. The key point of the survey was to get data about the consumption of “high risk food”.

Not surprisingly more men than women reported meat consumption, such as steak and rost, whereas women reported a higher consumption of fruits and vegetables. “High risk foods” such as runny eggs or raw austers were more frequently selected by male than by female individuals [63].

No sex differences were declared about cheese consumption. These data are conform with the findings of other studies such as the National Health interview survey of the years 1987 which demonstrated that women eat more fruits and vegetables, fewer high fat foods and less meat compared to men.

Women may have a higher awareness and knowledge of nutrition and healthy food patterns, even girls seem to have higher level of nutrition knowledge which may have an impact on food behavior [64].

4.1.2. Socioeconomic differences in food habits in Europe

Estevez et al. conducted a systematic review containing eleven studies from seven European countries in the period between 1985 and 1999 to examine consumption of fruits and vegetables among male and female individuals in

context to their level of education and occupation [65].
The data were achieved by food questionnaires and 24h-48h telephone recalls.
In summary the results suggest a positive correlation between a higher level of education or occupation and a greater consumption of fruit and vegetables [65].
Among the male group, the mean difference in the intake of fruit was 24,3 g/ person/ day between those with the highest level of education and those with the lowest.
Among the female group the difference was reported with 33,6 g/person/day.
Referring to the consumption of vegetables the mean difference between the male participants was 17,0g/day/person and 17,1 g/day/person between women [65].
Regarding former data education levels may influence the socioeconomic difference towards food behavior much stronger than occupation, income or employment status. Regarding the findings of Estevez, female participants reported higher fruit consumption than male persons and in generally, higher socioeconomic status was linked with a higher consumption of fruits and vegetables [65].

4.1.3. Gender differences in food choice: contribution of health beliefs and dieting

If we regard gender specific food patterns, health literacy and behavior are playing a key role as well as they do in pathogenesis of different diseases.
Wardle et al. conducted a review and examined gender differences in food choices in correlation with health beliefs and dieting.
Genderspecific health behavior is influenced by social structures; health protective behavior is often defined as female, the other way round health risk behavior is associated with masculine attitude [66,67].
Referring to gender specific food choices, it is well known, that boys and men have a lower consumption of fruits and vegetables, low fat foods and consume more soft drinks compared to female persons, six studies were mentioned in the review of Wardle in the period of the 90ies [66].
Women are supposed to concern more about weight control and dieting, independent from their age or their income.

“Femininity is often associated with lightness and delicacy in appetite” [66].

This statement defines the food behaviour, which is traditionally attributed to women. Four groups of food choices were examined in Wardle`s study by self-report questionnaire: avoiding fat, eating fibre, eating fruits and limiting salt.
The investigation includes 19289 university students at the age between 17 and 30 years, 10819 of the participants were female.
The results show that women have a higher consumption of fruits (OR 1,56) and high-fibre foods, lower consumption of high-fat foods and salt. Wardle et al. concluded that gender differences of food choice can be explained by the differences in health beliefs and by the fact that healthy eating is regarded as a female attitude [66,67].

4.1.4. TOSCA.IT

Sex- and genderspecific differences of food behavior and nutrition have an influence on prevalence and progression of diseases and disease related complications.
In front of this background the TOSCA.IT study was conducted to examine dietary behaviour among persons with T2DM and the effects on the lipid profile. In summary, 2573 people between the age of 50-75 were enrolled, 1535 male and 1038 female persons, the food habits were collected by the EPIC questionnaire [68].
The data of the study suggest that regarding the lipid profile, less women than men reached the therapeutic target of LDL less than 100, the female cohort showed a higher prevalence of metabolic syndrome, although HbA1c values were slightly better among women.
In summary the calorie intake from total fat and saturated fat was higher among the female participants, women had a higher consumption of fruits, vegetables, eggs, milk and vegetable oils, compared to men who had a higher consumption of starchy foods, soft and alcoholic drinks [68].
In fact, women reported a higher consumption of added sugar than men. 2,8% of

the females and 2,75% of the males didn't follow the nutrition recommendations for added sugar intake. Adherence to the recommended sugar consumption was associated with a more beneficial lipid profile, such as lower triglycerides and higher HDL fraction, this effect was also shown for the individuals without a lipid lowering medication. The detailed values are shown in the tables below [68].

Figure 3: adapted from Vitale M, et al., Sex differences in food choices, adherence to dietary recommendations and plasma lipid profile in type 2 diabetes - The TOSCA.IT study, Nutrition, Metabolism & Cardiovascular Diseases. 2016

Table 2 Nutrient composition of the diet and adherence to the nutritional recommendations in men and women with type 2 diabetes.

	Men	Women	Recommendations (DNSG [17]/SID [18])	Non adherence % (men $n = 1535$)	Non adherence % (women $n = 1038$)
Energy (Kcal/day)	1934 ± 674	1680 ± 593*			
Proteins (% of total energy)	18.3 ± 2.5	18.2 ± 2.5	10–20%	22.3 (343)	21.8 (226)
Fat (% of total energy)	36.4 ± 5.9	37.0 ± 6.1*	<35%	59.9 (920)	63.7 (661)*
SFA (% of total energy)	11.5 ± 2.5	12.0 ± 2.4*	<10%	81.8 (1256)	82.4 (855)*
MUFA (% of total energy)	17.7 ± 3.6	18.1 ± 3.9	10–20%	24.3 (373)	28.4 (295)*
PUFA (% of total energy)	4.4 ± 1.0	4.5 ± 1.1	<10%	0.4 (6)	0.8 (8)
Cholesterol (mg/day)	344 ± 148	304 ± 135*	<200 mg	85.6 (1314)	79.6 (826)*
Carbohydrates (% of total energy)	45.3 ± 7.1	44.8 ± 7.3*	45–60%	51.2 (786)	53.8 (558)
Added sugars[a] (% of total energy)	2.3 ± 3.2	3.4 ± 3.2*	<10%	2.7 (41)	2.8 (29)
Fiber (g/1000 Kcal/day)	10.4 ± 2.6	11.2 ± 2.8*	>15 g/1000 Kcal	94.8 (1455)	90.6 (940)*
Glycemic index (%)	51.8 ± 3.4	51.6 ± 3.2			
Glycemic load	123.0 ± 53.3	103.4 ± 42.6*			
Alcohol (g/day)	15.9 ± 17.9	4.0 ± 8.2*	<20 g for men and <10 g for women	0.8 (12)	0.2 (3)

$M \pm$ SD.
*$P < 0.05$ vs men.
DNSG (Diabetes and Nutrition Study Group); SID (Italian Diabetes Society).
[a] Soft drinks + sugar added by consumer.

Figure 4: adapted from Vitale M. et al. 2016

Table 3 Food groups (g/1000 Kcal/day) in men and women with type 2 diabetes.

	Men	Women
Starch (Pasta, Rice, Bread)	102.9 ± 37.0	95.2 ± 38.1*
Legumes	43.1 ± 38.8	48.7 ± 36.7*
Vegetables	87.6 ± 44.9	102.6 ± 50.3*
Fresh fruit	160.9 ± 88.8	190.6 ± 99.6*
Meat and salami	56.8 ± 26.1	56.2 ± 26.4
Fish	21.7 ± 16.5	23.8 ± 16.0
Eggs	10.6 ± 7.6	12.4 ± 9.1*
Dairy products	18.9 ± 12.6	19.4 ± 12.9
Milk and yogurt (whole)	27.8 ± 38.2	36.8 ± 44.1*
Milk and yogurt (low fat)	56.1 ± 77.3	76.7 ± 84.3*
Vegetable oils (condiment)	12.8 ± 5.5	14.6 ± 6.2*
Olive oil	11.4 ± 4.6	13.5 ± 5.7*
Other vegetable oils	1.3 ± 1.7	1.2 ± 1.9
Animal fats (condiment)	1.4 ± 1.5	1.2 ± 1.3
Cake and pastries	18.7 ± 18.7	20.2 ± 20.1
Soft drinks	17.9 ± 43.6	15.6 ± 37.5*
Sugar added by consumer	2.6 ± 5.3	4.3 ± 7.1*
Wine and beer	89.1 ± 92.3	24.6 ± 48.2*

$M \pm$ SD.
*$P < 0.05$ vs men.

Figure 5: adapted from Vitale M et al. 2016

Table 5 Plasma lipid profile by sex and adherence to the recommendations for intake of saturated fat (panel a), fiber (panel b) and added sugars (panel c) in population not on lipid lowering medications.

	Adherence		Non adherence		*P* for two-factors ANOVA		
	Men (n = 90)	Women (n = 62)	Men (n = 448)	Women (n = 289)	Sex	Adherence	Sex × adherence
Panel a							
HDL-cholesterol (mg/dl)	43.8 ± 10.8	48.0 ± 12.5	43.6 ± 10.5	49.6 ± 12.0	0.001	0.252	0.457
LDL-cholesterol (mg/dl)	109.4 ± 28.6	116.7 ± 32.0	115.9 ± 28.3	121.0 ± 29.3	0.021	0.049	0.656
Triglycerides (mg/dl)	157.1 ± 80.8	159.4 ± 80.8	153.3 ± 76.9	145.5 ± 66.4	0.464	0.124	0.544
BMI (kg/m^2)	29.7 ± 4.2	30.9 ± 5.4	29.9 ± 4.0	32.0 ± 5.2	0.001	0.141	0.309
	Adherence		Non adherence		*P* for two-factors ANOVA		
	Men (n = 31)	Women (n = 62)	Men (n = 509)	Women (n = 319)	Sex	Adherence	Sex × adherence
Panel b							
HDL-cholesterol (mg/dl)	46.5 ± 11.3	53.7 ± 12.1	43.4 ± 10.5	48.9 ± 12.0	0.001	0.142	0.254
LDL-cholesterol (mg/dl)	107.5 ± 20.3	118.4 ± 24.8	115.2 ± 28.8	120.5 ± 30.3	0.154	0.032	0.523
Triglycerides (mg/dl)	124.6 ± 55.4	134.1 ± 53.9	155.5 ± 78.2	149.3 ± 70.5	0.987	0.036	0.588
BMI (kg/m^2)	28.5 ± 3.9	30.1 ± 4.4	29.9 ± 4.0	32.0 ± 5.3	0.003	0.008	0.755
	Adherence		Non adherence		*P* for two-factors ANOVA		
	Men (n = 525)	Women (n = 341)	Men (n = 9)	Women (n = 8)	Sex	Adherence	Sex × adherence
Panel c							
HDL-cholesterol (mg/dl)	43.6 ± 10.6	49.4 ± 12.2	42.4 ± 12.2	45.3 ± 6.5	0.154	0.294	0.597
LDL-cholesterol (mg/dl)	114.7 ± 28.4	120.3 ± 29.9	118.6 ± 34.4	119.5 ± 25.6	0.547	0.252	0.780
Triglycerides (mg/dl)	152.3 ± 76.1	146.7 ± 68.7	252.2 ± 96.6	198.5 ± 80.1	0.056	0.001	0.216
BMI (kg/m^2)	29.9 ± 4.0	31.8 ± 5.2	29.8 ± 2.8	33.4 ± 6.3	0.013	0.481	0.440

4.1.5. Nutrition Survey among U.K. population

In addition to the findings of Wardle and the TOSCA.IT study, the results of a British survey (leading author Alan Beardsworth) after randomising 471 individuals (177 men, 244 women) between the age of 18 to 74 years describe sex and gender differences in food behavior in a larger intent [69].

The study participants were selected by telephone all and were asked by questionnaire similar to the Likert Scaling.

Some of the data were consistent with the findings of Wardle et al.

First of all more women than men reported a health consciousness related to their food choices. The selection of food categories also demonstrated a significant gender difference [69].

Female persons reported more often fruit and vegetable consumption (55,7% vs. 38,9% of the male persons for fruits, and 71,8% of females vs. 51,4% of males for vegetables), more women than men avoid red meat and more men than women reported consumption of crisps, fried foods and processed meat, meaning 53,7% of men compared to 30,7% of women.

Some categories such as white meat, starchy foods or chocolate didn't achieve gender differences, which is different to the results of the TOSCA.IT study, which suggested a higher consumption of starchy foods among male persons.

Furthermore more women than men declared vegetarian food behavior (5,3% vs.

1,7%) [69].
The point of health and weight concerns and self-perception is stronger represented among women. A higher proportion of female persons reported dietary strategies or changes to alter or reduce weight (16,8% vs. 7,9%) [69].

4.1.6. Framingham Nutrition Study

The Framingham Nutrition study includes a subsequential investigation in the so-called Framingham Offspring and Spouse study (FOS) with 590 normalweight American women between the age of 25 and 71 years over a period of 16 years [70].
Dietary behavior was assessed with the Framingham Nutritional Risk Score and nineteen nutrients including total energy, protein, total fat, quality of fats, carbohydrate, fibre, alcohol, vitamins and trace elements were assessed.
The findings suggest that females with the lowest diet quality have lower consumption of carbohydrate, fibre and micronutrients (except vitamin B12), but higher consumption of alcohol and total fat. Women with higher quality of food habits were older and with majority non-smokers [70].
The data suggest a correlation between the risk of overweight and obesity and level of diet quality, the incidence of overweight and obesity over 16 years of investigation was reported by 44% of the study population.
Women with higher protein consumption also reported a higher carbohydrate and fat diet and were at higher risk for becoming overweight. Higher energy, fibre and vitamin E consumption were inversely associated with the risk of overweight and obesity [70].

4.1.7. German Nutritional Survey II

The results of the German National Nutrition Survey II gave an overview over food consumption and dietary behavior as well as life styles in correlation with socio-economic status of German adults between the age von 14-80 years [71].
The study includes 15371 subjects in the period between November 2005 and November 2006, the data were assessed by personal interviews and self-

administered questionnaires, anthropometric parameters such as body weight and height were measured. The social class index was defined by regarding income status, education level and employment status. 7093 persons of the study population were male, 8278 were female.

In the following part the results for the different food groups are summarized:

Women reported a slightly higher consumption of fruits, vegetables, vegetable products than men, the amount increases for both sexes at the age group of 51-64 years, women consumed more raw vegetables than men, in generally the consumption of vegetables didn't reach the recommended amount of nutrition guidelines [71].

The consumption of milk, dairy products and cheese was higher among male persons than women at the age of 14-50 years, in the age group over 51 years there was no difference.

Concerning consumption of meat, meat products and sausages, men reported a twice as high amount than women. Men of all age groups exceeded the DGE guidelines, which recommend 300-600 g/day [71].

Food choices regarding fats and oils of animal or vegetable origin showed a higher consumption among men than in women, but the reported amount fulfilled the recommendation dose of the DGE [71,72].

The consumption of sweets, dessert, ice cream and sweeteners was higher in men than in women, in totally the consumption of both sexes was higher in the age group of 14 - 50 years than in the older group [71].

The male participants reported a 2,5 times higher consumption of soft drinks compared to the female study members, whereas the amount of beer consumption was six times higher.

Higher socio-economic status in both sexes was associated with higher consumption of cereals and cereals products, but lower consumption of potatoes, higher consumption of vegetables fruit and fish, lower consumption of meat and meat products.

Individuals with higher socio-economic status reported a higher preference of water, coffee and tea, and a lower preference of soft drinks.

Regarding alcoholic beverages they preferred wine to beer. In totally women of all age groups and elder people reported healthier food choices than men and

younger adults, higher socio-economic status was correlated with a healthier food selection [71].
Compared to nutrition surveys of other European countries German people seem to have the highest consumption of bread, fruit juices and nectars and beer [70].
Arganini et al. suggested in their review that gender differences in food choices in modern western societies mainly rely on eating habits, health consciousness and dietary behaviour with the desire for weight control, which means that different motivation triggers food behavior among men and women, related to age [73].

The question arises at which age gender differences in food behavior emerge.
During the adolescent period, at the age between12-17 years, girls already spend more attention to food choices than boys, 62,5% of girls compared to 55,9% of boys [74].
Women more frequently consume snacks than men, they prefer fruits and yoghurt whereas men prefer fruits and savory snacks [74].
One essential fact to describe female dietary patterns is that women more often have an ambivalent relation to food, for men exercise and sport are more important to maintain health [74].
It is well known that women prefer dietary strategy to control their weight, men are more likely to practice exercise, twice as many female than male adults are undergoing a diet [74,75,76].

4.1.8. Food behavior and risk for NAFLD

The association between food behavior and the risk for NAFLD was investigated by Zelber-Sagi et al. in a cross sectional study of a subpopulation of the Israeli National Health and Nutrition Survey, 347 adults between 24-70 years were included, 52,7% were male persons. Dietary assessment was performed by a semi-quantitative food questionnaire, NAFLD was diagnosed by biochemical tests and sonography [77].
Women with NAFLD had a higher calorie intake than healthy women.
The daily carbohydrate consumption of sweet foods among participants with NAFLD was as twice as high compared to the persons without NAFLD, the protein

consumption of all types of meat was increased by 27% [77].
Uric acid and plasma cholesterol levels were higher among the “NAFLD group”.

The results suggest that a higher intake of soft drinks and meat was associated with an increased risk for NAFLD, while consumption of fish, containing omega-3 may reduce the risk, independent of age, BMI and gender [77].
An interesting fact regarding genderspecific food behavior is, that women with NAFLD reported a higher calorie intake than men with NAFLD. One explanation could be a higher awareness of serving sizes and calories among women [77].
The role of fructose in the pathogenesis of NAFLD is intensively discussed in recent literature. A pilot study to examine the association of fructose consumption and prevalence of histologically diagnosed NAFLD was performed by Ouyang et al. [78].
The study population contained 49 persons with biopsy-proven NAFLD and 24 with negative liver biopsy. Daily fructose consumption was assessed for a period of three months, serum markers such as lipid profile, uric acid and serum glucose were analysed. Uric acid and plasma cholesterol levels were higher among the NAFLD group. The results showed that persons with NAFLD reported a higher daily fructose intake than healthy persons, 365 kcal/day vs. 170 kcal/d. The study data are consistent with the data of Mc Carthy et al. [78,45].
Further discussion is necessary to point out if there is a difference between the dietary fructose sources in relation to pathogenesis of liver disorder.

4.1.9. Helsinki Birth Cohort study

A Helsinki Birth Cohort Study included 1611 male and female persons, born in 1943-1944, for a period of three years (2001-2004).
Dietary behavior over the last 12 months was assessed with a validated food frequency questionnaire (FFQ), the presence of NAFLD was determined by fatty liver index (FLI) which contained BMI, waist circumference, fasting triglycerides and y-glutamyl-transferase (GGT), and the NAFLD liver fat score, which was based on presence of diabetes, metabolic syndrome, fasting insulin, serum aspartate aminotransferase and alanine aminotransferase ratio [79].

663 subjects (44% of the study population) were affected by NAFLD by using FLI (fatty liver index) as diagnostic kit, whereas 511 subjects (=46%) were diagnosed by using the NAFLD liver fat score.

The findings of the Cohort Study suggest that women reported higher fructose consumption than men. Individuals of the category with the highest quartile of fructose intake had a higher level of education and physical activity as well as a higher intake of fibres and lower intake of fat and they were less likely to be smokers compared to the individuals of the category with the lowest fructose intake [79].

Surprisingly the prevalence of NAFLD among the group with the highest fructose consumption was 28-44% lower than in the group with the lowest fructose intake. The average fructose intake was 20g/day, only 60 persons reported a fructose intake more than 60g/day. The cohort study provides no available data about the different fructose sources [79].

Table 1: Comparison of the nutrition study trials

abbreviations: m=male; f= female; a= age

study	duration	population	sex	ethnicity	methods
FoodNet Survey	May 2006-April 2007	14878 >18a	38% m 62% f	US population	telephone 7 days
Estevez 11 studies	1985-1999	18-85a	both sexes	15 European countries	dietary recall 24-48h
Wardle et al.	1999-2001	19289 students	8482 m 10816 f	23 countries	IHBS
TOSCA.IT subanalysis	48 months	2537 50-75a	1535 m 1038 f	60 centres Italy	EPIC
Framingham Nutrition studies	16 years follow up	590 25-71a	590 f	US population	FNRS dietary recall 3 days
German Nutritional Survey II	2005-2006	15371 14-80a	7093 m 8278 f	German population	dietary recall 4 weeks
Beardsworth et al.	2002	471 18-74a	177 m 244 f	U.K. population	Likert Scaling interviews
Helsinki Birth Cohort Study	2001-2004	1611 >60a	both sexes	Finnish population	FFQ

5. Discussion

NAFLD seems to be the liver disease of our age. If we regard the recent data of increasing prevalence it may rise to a threat to global health. NAFLD is associated with a higher cardiovascular risk and risk of overall morbidity.

Furthermore it is one of the leading causes of endstage liver damage, 2009 9,7% of liver transplantations were caused by NAFLD [8,9].

Referring to the data of the EASL/EASD/EASO Guidelines the prevalence of NAFLD among adults in Western countries is reported with 17-46% [15]. The guidelines recommend sonography as first diagnostic step in clinical practice, supported by biochemistry and diagnostic scores. On the one hand 70% of persons with NAFLD have normal levels of ALT and AST, on the other hand ultrasound has its limitations as diagnostic tool [16].

Ethnicity plays an important role in the presence of fatty liver, Hispanics and Asian people have a particularly high risk of being affected by NAFLD [6,7].
NAFLD is strongly linked with the features of the metabolic syndrome and the positive association of obesity, T2DM and NAFLD is well known [3].
The results of the Austrian Diabetes Report 2013 report a prevalence of diabetes among 8-9% of the Austrian population, while 2-3% are not recognised [80]. Socioecoomic status and education level are negatively correlated with the presence of T2DM, particularly among women a lower social status means a higher risk of T2DM. People with migration background have a overall higher risk of chronic diseases. Female migrants in Austria have 3,4 fold higher risk of developing T2DM, while male migrants have a 1,4 fold higher risk [81,82].
If we additionally consider the prevalence of NAFLD among persons with T2DM with 70%, individuals with migration background are a susceptible risk group for the cluster of metabolic diseases.

Regarding the prevalence of NAFLD among pre- and postmenopausal women, there are reliable data, which indicate a high risk for postmenopausal women and women with PCOS for being affected by NAFLD. Marino et al. reported in their review a prevalence of NAFLD in association with PCOS with a range between 15 to 71%. The range of variation is caused by the use of different diagnostic tools [21].
PCOS is associated with overweight and insulin resistance, but the fact that 39% of normalweight women with PCOS are affected by NAFLD suggest PCOS as an independent risk factor for NAFLD [20].
Sexual hormones play a role in pathogenesis of NAFLD in correlation with interaction of different adipokines and cytokines and their effects on lipid

metabolism.

Which are the clinical features of male vs. female NAFLD?

Male NAFLD is characterised by higher ALT levels, higher adiponectin and lower leptin levels as well as greater visceral adipose tissue thickness than women [22]. Women with hyperandrogenism have higher transaminase levels, independent from their bodyweight. Regarding the recent data the role of leptin as potential promotor of hepatic steatosis and fibrosis severity remains unclear [21].

With growing age in the postmenopausal period estrogen levels and subcutaneous adipose tissue decrease in favour of visceral adipose tissue and are related to further change of adipokine levels, which mediate lipid metabolism and inflammation. Visceral adiposity is connected with postmenopausal age [27].

These facts define postmenopausal women and women with PCOS as a high risk population and implicate the need for early screening strategy, even if we refer to the links between NAFLD and extrahepatic complications such as cardiovascular diseases.

If we discuss gender aspects of NAFLD and their relevance for cardiovascular morbidity it must be taken in consideration that there are reliable data which indicate the elevation of ALT levels as a surrogate parameter for coronary heart diseases among men, but not among women, obviously caused by the fact, that female NAFLD doesn`t necessarily mean a change of liver enzymes.

The combination of estrogen deficiency and relative androgen excess and furthermore the dominance of visceral fat with rising insulin resistance define the pathogenesis of NAFLD among postmenopausal women [39].

The guidelines currently contain no recommendations for screening peri- and postmenopausal women for subclinical NAFLD [81].

Do we need comprehensive screening programs for healthy female individuals to diagnose subclinical NAFLD and establish a targeted health care?

It is well known that dietary behavior and food habits play an important role in the

pathogenesis of various diseases.

The result of the present literature overview suggest, that persons with NAFLD have a higher consumption of saturated fats and cholesterol and lower amount of fibres, antioxidants and polyunsaturated fats [45].

Furthermore a higher daily fructose intake is reported among individuals with NAFLD [45,78]. Fructose is frequently discussed to be a promoter in the pathogenesis of NAFLD.

Fructose consumption has risen over the last decades parallel with the growing epidemic of obesity, the main sources of fructose intake come from sucrose and high fructose corn syrup in industrialised products, much less from fruits [45].

The pathophysiologic mechanisms and pathway of fructose were mentioned in the text above.

Summarizing the controversial data about whether fructose consumption is a strong promoter for pathogenesis of NAFLD, it is important to recognize that there are no large prospective observational studies among humans to investigate the correlation between fructose intake and NAFLD [54].

Furthermore it is well known that in contrast to the rodent model de novo lipogenesis from fructose provides less than 1% of fatty acids in humans, whereas animal studies reported that 70% of fatty acids are metabolized by de novo lipogenesis. Glucose-, lactate- and glycogen synthesis are the dominant pathways of hepatic fructose disposal [54].

At this point of view the metabolic side effects of fructose consumption must be discussed in relation to the total calorie intake and in relation to the amount of other macronutrients.

Supporting the gender approach towards NAFLD, the results of Couchepin et al. suggest that the impact of fructose consumption on lipid metabolism such as elevation of triglycerides is lower among premenopausal women than men.

This may indicate once again the protective metabolic effects of female sex hormones [57]. However there is a lack of knowledge about the impact of fructose intake on serum lipids among postmenopausal women.

Do female and male dietary patterns differ?

The comparison of eight study trials, including two surveys with more than 10000

participants and one trial with a follow up for 16 years, gives an overview about characteristics of female dietary profile:
Women have a higher consumption of vegetables and fruits, but a lower consumption of meat and high fat foods than men. Men report a higher consumption of starchy foods and red meat, soft drinks and alcoholic drinks. These results were consistent in the different study trials.
Estevez et al. described the positive correlation of higher socioeconomic status with the consumption of fruits and vegetables, whereas Wardle et al. pointed out the gender differences in health belief and awareness [65,66].
The data of the German Nutritional Survey report changes of dietary behavior in relation to age [71].
Study participants of both sexes at the age between 51 and 64 years reported a higher consumption of vegetables and fruits, but a lower consumption of sweets, dessert ice cream and sweeteners, whereas the intake of sweet foods was higher among men in all age groups [71].
In totally women of all age groups reported healthier food choices, higher socio-economic status was correlated with healthier food selection.

Zelber-Sagi et al. examined in their cross sectional study the correlation of nutritional intake and risk of NAFLD. The female participants reported a higher calorie intake than the male persons [77].
The individuals with NAFLD had a twice as high carbohydrate consumption of sweets compared to the healthy group and increased meat consumption by 27%. Women with NAFLD reported a higher calorie intake than men with NAFLD.
This could be explained by the fact, that women have more awareness to serving sizes, energy density and calories than men, probably, a reporting bias of over- and underreporting must be assumed.
Ouyang et al. demonstrated in their pilot study the correlation between daily fructose intake and histologically diagnosed NAFLD as well as serum markers (lipid profile and uric acid) [78].
The findings show a higher daily consumption of fructose among the participants with NAFLD compared to the participants with negative histology, 365 kcal/day compared to 170 kcal/die. One point to argue is the lack of data to differentiate the

fructose sources, whether the fructose comes from fruits or sucrose and high fructose corn syrup, because of the small size of study population there are no reports about sex differences regarding calorie intake or histological graduation.
A recent Finnish Cohort study presents interesting findings about the correlation of fructose consumption and prevalence of NAFLD.
The participants, who reported the highest fructose consumption, had a lower prevalence of NAFLD and made healthier food choices than the individuals with lower fructose consumption [79]. Female study members had a higher fructose intake than the male persons, the average fructose intake was reported with 20g/day [79].
Comparing these results with the data of Chiu et al., there is a big difference between the amount of daily fructose consumption with potentially metabolic effects: ⩾50 g/day for postprandial triglycerides, >100g/day for fasting triglycerides [54,79].
In the debate about the negative metabolic effects of fructose consumption, it is much more necessary to differentiate the fructose sources and the total amount of energy intake as well as the relation of proteins, saturated and not saturated fats and total carbohydrate intake.
Discussing female dietary patterns and their influence on disease development the data of the literature research provide no evidence that female dietary strategies contribute to the rising prevalence of NAFLD.
In contrary women may have a higher level of health literacy and health protective behavior than men, and often have more concerns about weight control.
Especially the data of the German nutrition survey emphasize that women of all age groups have healthier food behavior than men. Women prefer dietary strategies to reduce weight, while men prefer exercising [66,74,75,76].

6. Conclusion

NAFLD can be precursor as well as part of the metabolic syndrome and is often associated with obesity and T2DM.
Persons of all age groups can be affected by clinical or subclinical NAFLD, but

postmenopausal women, women with decreased estrogen levels (PCOS, premature menopause) as well as men with testosterone deficiency (aging men, men with hypogonadism) are at particularly high risk. Furthermore NAFLD is a chronic liver disease without an age limit.

In context to worldwide epidemic of growing obesity we can expect a rising prevalence of NAFLD also among children and adolescents, recent data describe a disease prevalence of 36-44% among European obese children and young adults [2].

First of all we must create the awareness for NAFLD as an essential cardiovascular risk factor.

As a consequence early screening procedures for high risk individuals should be evaluated.

There is the need for further investigations, especially prospective observational studies, about the influence of different fructose sources on pathogenesis of NAFLD. Furthermore sex- and genderspecific statements in nutrition policy guidelines should be established. Nutritional support with the recommendation for a balanced diet, physical activity and weight reduction are the main therapeutic tools.

The S3 DGEM guidelines contain no detailed recommendation about carbohydrate intake for NAFLD [83].

The “EASL Clinical practice guidelines” declare that “dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components such as processed food, and food and beverages, high in added fructose” [15].

The S2k Guidelines for non-alcoholic fatty liver disease from the year 2015 indicate that there is no need for a comprehensive screening for NAFLD in adults, only persons who are at high risk for NAFLD should be screened by sonography and measurement of liver enzymes [84].

What are the implications for the clinical practice?

First of, all we must raise the awareness of NAFLD among health professionals.

Individuals with an increased risk for NAFLD should be screened with sonography

and liver enzymes, with a genderspecific approach in mind to achieve, that NAFLD as the leading cause of chronic liver disease no longer remains under-recognized. Angulo et al. referred in their review to a diagnostic algorithm, which could be useful in daily clinical practice to identify persons with subclinical hepatic steatosis in relation to their comorbidity.

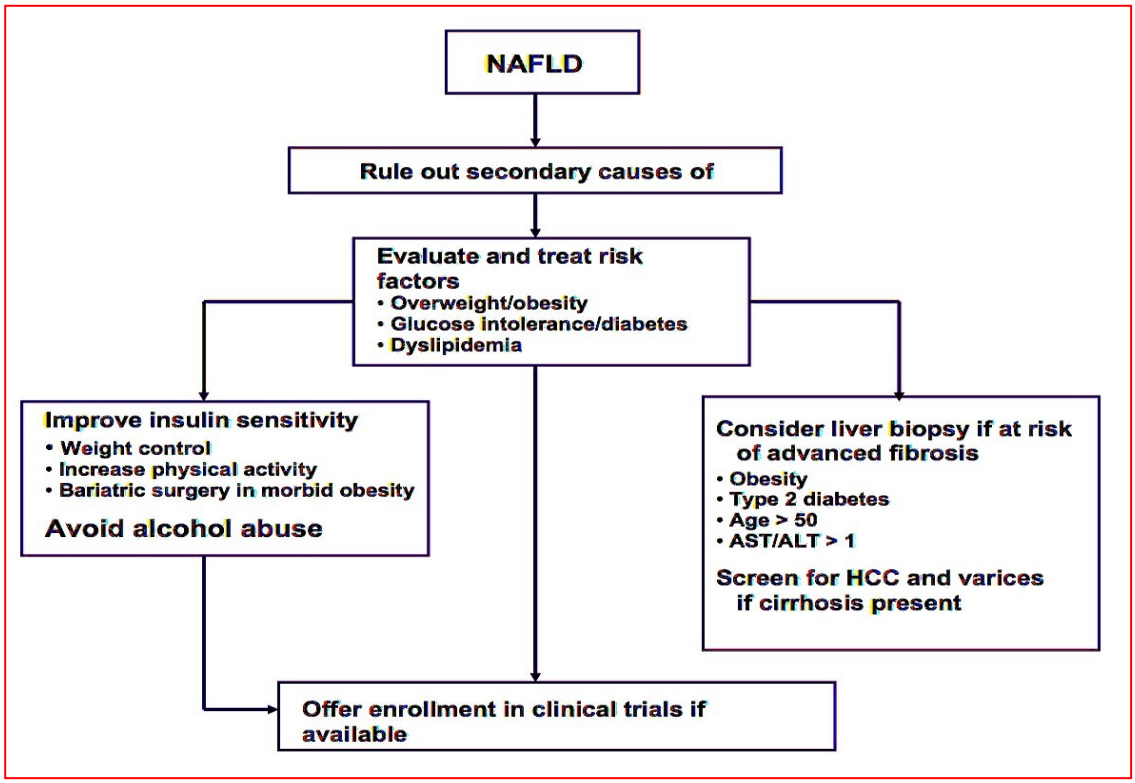

Figure 6: diagnostic algorithm, adapted from Angulo P., Obesity and Nonalcoholic Fatty Liver Disease. Nutr Rev. 2007;65(SUPPL.1).

An essential point in the algorithm is the early treatment of concomitant metabolic risk factors with focus on weight reduction and early screening for prediabetes and T2DM. NAFLD is a crucial indication for the performance of a glucose tolerance test and should be implemented as a screening criterion in the valid guidelines of the Diabetes Societies.

The currently valid nutritional recommendations are listed in the “EASL practice guidelines” already mentioned. They include the statement of the American Heart Association to limit daily sugar intake with 100 kcal/ day for women and 150 kcal /day for men.

Nutritional support and lifestyle intervention with focus on physical activity and weight reduction are the basic therapy tools. Regarding the development of NAFLD over the past decade, targeted prevention strategy and early diagnosis are the challenge for interdisciplinary medical care and health system as well as providing extensive information to raise the awareness for NAFLD as a potential systemic disease with an increased overall mortality.

7. Conflict of interest

There is no conflict of interest to declare.

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