REVIEW

Available from: http://www.jgld.ro/wp/archive/y2015/n3/a13
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.243.gta

Hype or Reality: Should Patients with Metabolic Syndrome-related NAFLD be on the Hunter-Gatherer (Paleo) Diet to Decrease Morbidity?

Giovanni Tarantino[1,2], Vincenzo Citro[3], Carmine Finelli[4]

1) Department of Clinical Medicine and Surgery, Federico II University, Medical School of Naples, Naples;
2) Centro Ricerche Oncologiche di Mercogliano, Istituto Nazionale Per Lo Studio E La Cura Dei Tumori Fondazione Giovanni Pascale, IRCCS, Mercogliano (Av);
3) Department of Internal Medicine, Umberto I Hospital, Nocera Inferiore, Salerno;
4) Center of Obesity and Eating Disorders, Stella Maris Mediterraneum Foundation, C/da S. Lucia, Chiaromonte, Potenza, Italy

Address for correspondence:
Giovanni Tarantino
Department of Clinical Medicine and Surgery
Federico II University Medical School of Naples
Via Sergio Pansini, 5,
80131 Naples, Italy
tarantin@unina.it

Received: 20.06.2015
Accepted: 28.07.2015

ABSTRACT

The current Western diet figures centrally in the pathogenesis of several chronic diseases such as obesity, type 2 diabetes, cardiovascular disease and the emerging major health problem nonalcoholic fatty liver disease, all of them negatively impacting on life expectancy. This type of diet is represented by a high calorie uptake, high glycemic load, high fat and meat intake, as well as increased consumption of fructose. On the contrary, a simplified way of eating healthily by excluding highly-processed foods, is presumed to be the Paleolithic diet (a diet based on vegetables, fruits, nuts, roots, meat, organ meats) which improves insulin resistance, ameliorates dyslipidemia, reduces hypertension and may reduce the risk of age-related diseases. The diet is the foundation of the treatment of obesity- and type 2 diabetes-related nonalcoholic fatty liver disease and a diet similar to those of pre-agricultural societies may be an effective option. To lend sufficient credence to this type of diet, well-designed studies are needed.

Key words: NAFLD – Paleo diet – metabolic syndrome – obesity.

Abbreviations: BMI: body mass index; BP: blood presure; CHO: carbohydrates; CVD: cardiovascular disease; FAs: fatty acids; FFAs: free fatty acids; HDL: high-density lipoprotein; HG: Hunter-gatherer; IIS: insulin/IGF-1 signaling; IOM: Institute of Medicine; LDL: low-density lipoprotein; MUFA and PUFA: mono- and polyunsaturated fatty acids; MS: metabolic syndrome; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; PAI-1: plasminogen activator inhibitor-1; RNS: reactive nitrogen species; ROS: reactive oxygen species; HNE: 4-hydroxy-2-nonenal; MDA: malondialdehyde; SF: saturated fat; TFI: total fiber intake; T2DM: type 2 diabetes mellitus; VLDL: very low density lipoproteins.

INTRODUCTION

Our ancestors, belonging to the pre-agricultural epoch, the so-called Hunter-Gatherer (HG) during the Paleolithic age, also known as stone age, starting from about 2.5 million to 10,000 years BC, fed mainly on meat, organ meats and insects, roots, green vegetables, seasonal fruit and nuts, as reported by Boers et al. and Cordain et al. [1, 2]. This type of diet, labeled as the Paleolithic diet, has been suggested, but with some criticism by some authorities [3], to concord better with our evolutionary inheritance than a diet built on agricultural products available during the Neolithic period (nearly 10,000 years BC – nowadays), i.e., grains and dairy products [1, 4, 5]. A diet discordant with our evolutionary inheritance is thought to determine illnesses due to an inadequate re-arrangement [1, 6]. The lower incidence of those diseases, assumed to be from affluence [1, 7], such as obesity and type 2 diabetes mellitus (T2DM), with the related nonalcoholic fatty liver disease (NAFLD), as well as cardiovascular disease (CVD) among non-Western populations can be justified by assuming HG-similar diets but also having an equal lifestyle [1, 8, 9]. It should be emphasized that the supposed factors, i.e., fat (both amount and quality) and (cereal) fiber, claiming lower incidence of diseases of affluence, have little impact on mechanisms inducing such diseases [1, 10]. A potential mechanism is more likely to be that the Paleolithic diet opposes impaired glucose homeostasis, i.e., the insulin resistance, considered a factor central to NAFLD, and hypertension [1, 4]. Obviously, food scarcity coupled

with the accompanied decreased food consumption as well as the satiating properties of a Paleolithic diet [1, 4] could play a certain role. Caloric restriction of 20–40% of dietary energy opposed to free feeding (ad libitum) has been demonstrated to reduce the incidence of several diseases of affluence in non-human primates, and possibly human beings [1, 11]. Interestingly, non-Western populations with HG lifestyle and diet show no tendency to obesity and acquire health benefits, perhaps a slowing aging process, in the same way of those obtained by caloric restriction despite the ad libitum availability of food [1, 12].

In many reports, scholars compared the HG diet, or that presumed to be, to an a-specific modern diet, often accounted for as a Western diet. Moreover, from the study of the eating habits of the populations bordering the Mediterranean Sea, it was possible to define the healthier Mediterranean diet (Table I) [13].

DIFFERENCES BETWEEN MODERN WESTERN AND HUNTER-GATHERER DIETS

Dietary Fat and Cholesterol

Cholesterol is one of the main components of the phospholipid bilayer of the cell membrane in animals. Moreover, muscle cell membranes have a similar cholesterol content as adipocytes [14]. Dietary phospholipids, which are found in high amounts specifically in game meat, have been shown to inhibit cholesterol absorption, as reported by Igl et al. [15].

Despite the increased cholesterol intake (HG cholesterol intake is estimated at 480 mg/day, nearly 200 mg/day higher than recommendations), the main source of cholesterol is lean meat and fish, which have anti-atherogenic properties [3, 16]. There is no evidence, until now, that lean meat (similar to wild game) intake corresponding to the levels in the average HG diet has adverse health consequences. Therefore, in this case the paradigm of the association between diet high in meat - and therefore cholesterol - and atherosclerosis is questioned. A better strategy is to maintain serum cholesterol and low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio to optimal levels and maybe to restrict intake of cholesterol-raising fatty acids and dietary refined carbohydrates [17]. Mensink et al. [18] have suggested that the effects of dietary fats on total HDL cholesterol may differ markedly from their effects on LDL.

The increased intake of saturated fat (SFA), and especially C-14 and C-16 fatty acids, i.e., tridecanoic acid and tetradecanoic acid, is a major contributor to atherosclerosis. The first and third leading causes of death in industrialized countries are CVD and stroke, atherosclerosis being associated with each one. Moreover, in a modern diet the SFA intake and total fat intake - the range proposed in dietary guidelines for SF is 7–10% of energy and for total fat 20-35% of energy, respectively, is far too high and contributes also to the propagation of endemic obesity and T2DM [19]. However, the basic risk factor of the obesity epidemic is the positive energy balance and not the increased fat intake. There are also high fat patterns (e.g. the Mediterranean type) that are inversely correlated to obesity and T2DM incidence.

In the HG diet total fat contributes to about one third of the total daily intake of calories [20], in concordance with recommendations that the total fat intake should not be below 30%, the main target consisting of having low SFA [21]. Very low total fat percentage may prevent, delay and almost totally reverse atherosclerotic plaque formation [22].

The Instute of Medicine (IOM), beyond suggesting a HG diet, recommends that SFA intake should contribute to a maximum of 10% of total energy, any increase being related to CVD risk [23]. The proposed diet with decreased content in SFA is considered by epidemiologists as an equivalent of diet rich in mono and polyunsaturated fatty acids (MUFA and PUFA). It should be noted that game animals and marine animal flesh have more MUFA and PUFA than beef, chicken, pork and other meats commercially available [17, 23]. There are well-known dissimilarities in commercial farming, differently affecting MUFA content [24].

The amount of PUFA ingested by ancestral people is estimated to be higher than in the standard modern diet, and it is almost completely due to a greater proportion of cardio-

Table I. Comparison of diets

	Hunter-gatherer	Traditional Mediterranean	Traditional low-fat (Ornish diet)	Low-carbohydrate (Atkins diet)
Carbohydrates (%)	Moderate (22-40)	Moderate (50)	High (80)	Low (4-26)
Total fat (%)	Moderate (28-47)	Moderate (30)	Low (<10)	High (51-78)
Saturated fat	Moderate	Low	Low	High
Monounsaturated fat	High	High	Low	Moderate
Polyunsaturated fat	Moderate	Moderate	Low	Moderate
Omega 3 fat	High	High	Low	Low
Protein (%)	High (19-35)	Moderate (16-23)	Low (<15)	Moderate (18-23)
Total fiber	High	High	High	Low
Fruits and vegetables	High	High	High	Low
Nuts and seeds	Moderate	Moderate	Low	Low
Salt	Low	Moderate	Low	High
Refined sugars	Low	Low	Low	Low
Glycemic load	Low	Low	High	Low

protective ω-3 fatty acids. In this case, HG diet may be very restrictive compared to current recommendations [17, 25].

Carbohydrates

Carbohydrates (CHO) are the first source of energy (accounting for more than 50% of daily energy) specifically, in the American diet and, generally speaking, in the Western diet (Table I). Added sugars (any type) account for 15% of energy intake [3, 26]. Meanwhile, 85% of cereal grain, in Western diet, are refined and represent the largest single CHO source [3]. It is also important to note that dairy farm products are significant contributors to the total sugar intake [27]. The amount of sugar in a modern Western diet is higher than in the HG diet. In the latter, the majority of CHO comes from fruits and vegetables, deriving only 2-3% from honey (added sugar) and probably none from refined cereal grains [3, 23, 28]. Following the HG diet, the IOM recommendations are fulfilled (CHO ranging from 45% to 65% of total energy). Moreover, the proportion of added sugar drops from 25% in the American/Western diet to 3% in the HG diet [3, 26]. It is noteworthy to stress that the Mediterranean diet is relatively high in sugar derived from cereal grains, when compared to the HG diet, surprisingly resulting in being less effective in improving insulin resistance and CVD risk factors in T2DM subjects [3, 29].

Such recommendations are shifting toward the ancestral example (Table II), as reported by Eaton et al. [30].

Protein

Since the 1980s, a reduction in the percentage of protein intake, particularly meat-derived, and a rise in SF consumption, has been clearly evidenced in the modern Western diet [31].

According to a recent theory, a rich-in-meat diet might be harmful to health because it leads to an excessive nitrogen load [31, 32]. Moreover, since the 1980s experts have advised pursuing a reduction in protein intake, particularly meat derived, due to its association with high cholesterol-raising fat intake [31, 32].

Conversely, HG diet is rich in protein (25-30% of total energy intake versus 16% in the US diet), especially deriving from wild game and aquatic species. Actually, there is no evidence that the quantity of wild game, or similar lean meat, consumed in levels corresponding to those of the HG diet has adverse health consequences.

Sodium and the Sodium/Potassium Ratio

The INTERSALT study showed a positive relationship between dietary sodium intake and blood pressure (BP) [33].

As clearly described in Table II, there are important differences from the HG diet and the modern Western diet in sodium and potassium intake.

A relevant limitation in studying the HG diet is that it is difficult to directly compare the long term effects in a real population. However, we may consider modern populations having a sodium intake near that range estimated for ancestral HG. Populations with very low urinary sodium excretion (0.9 mmol/d) have a mean systolic/diastolic blood pressure of 95.4/61.4 mm Hg, with no registered cases of hypertension and BP not increasing with age [34].

A WHO meta-analysis [35], which excluded very low salt intake populations, concludes that reduction of sodium intake to less than 5 g/day is correlated to a reduction of 17% in the overall rate of CVD and 23% of stroke, ultimately preventing

Table II. Comparison of recommendations

		Recommendations	
	Estimated ancestral intake	**Pre-1990**	**Current**
Nutrients			
Carbohydrate (% daily energy)	35-40	55-60°	45-65
Added sugar (% daily energy)	2	12	<25
Fat (% daily energy)	30-40	30	20-35
Satured fat (% daily energy)	7.5-12	<10	<7
Cholesterol (mg/d)	≥500	<300	<300
EPA+DHA*	5-6	-	1.6 for males, 1.1 for females
Protein (% daily energy)	25-30	10-15	10-35
Fiber (g/d)	>70	-	38 for males, 25 for females
Vitamin C (mg/d)	500	60	90 for males, 75 for females
Vitamin D (IU/d)	4000 (sunlight)	400	1000
Calcium (mg/d)	1000-1500	800	1000
Sodium (mg/d)	<1000	2400	1500
Potassium (mg/d)	7000	2500	4700
Body composition (% lean:% fat)			
Females	35-40:20-25	-	<31% fat
Males	45-50:10-15	-	<26% fat
Physical activity (Kcal/d)	> 1000	-	150-490

° Range (all such values); * EPA+DHA, eicosapentaenoic acid + docosahexaenoic acid

more than 4 million deaths worldwide every year. Subsequent studies found that a 25-35% reduction in salt intake reduces the risk of CV events of 25% in a follow-up period of 10-15 years and a validated computer simulation evidenced that the passage from the estimated actual 10.4 and 7.3 g/d of salt for adult males and females reduces linearly CVD mortality [36, 37].

Following a HG diet nowadays does not simply ensure a low salt/sodium intake.

Electrolyte and Acid Base Balances

Low consumption of potassium-rich fruits and vegetables with an increasing added sodium intake (roughly 10 fold higher than in HG) such as in the Western diet results in sodium levels exceeding potassium levels [38]. These modifications in combination with the high consumption in cereal grains and dairy products would drive systemic pH toward acidity [3, 39]. Exaggerated urinary calcium, bone calcium depletion, nephrolithiasis, loss of muscular mass and renal insufficiency are the dramatic consequences and imply corrective measures against diets favoring metabolic acidosis [3, 40]. Ströhle et al., studying four different models of animal fat densities (model A, 3%; model B, 10%; model C, 15%; model D, 20%) confirmed that the net endogenous acid production of HG diets shifts progressively from negative to positive as plant-to-animal ratios decline, and nevertheless, tends to increase compared to the western diet [39]. The HG diet, which had for the most part plant based alimentation (such as that of ancestral East African populations), would have had a more favorable net negative acid load, confirming the suggested overall alkaline net load for HG diets [3, 6, 39].

The acid-base hypothesis has been proposed to affect bone metabolism but results remain inconclusive. On the contrary, HG calcium content is vague and, looking at Table I, could range from adequate to very low.

THE PREHISTORIC QUESTION

Several studies focused on the development of a model of HG diet. Moreover, the principal difficulty in accomplishing this task is that there is a high dietary diversity among populations, as noted for modern HG societies [6]. Cordain et al. [27] estimated macro-nutrients energy and plant to animal ratio (the latter aimed at evaluating whether HG diets were predominantly based on animal or vegetable food) on the data from Murdock's Ethnographic Atlas and found that 73% of the worldwide HG societies derived > 50% of total daily energy from animal foods and only 14% used more gathered plant foods. These discrepancies are at the basis of another important macro- and micro-nutrients intake, as fibers and minerals.

The IOM suggests a minimum daily fiber intake of 25 g/d for women and 38 g/d for men, but the current median intake is about half of this (15.5 g/d for women and 18.7 g/d for men) in the US and only in the South and Central-East Europe does it nearly reach the recommended intake (Table I) [3, 24].

In a review by Konner and Eaton [3], the authors published the results of the most recent estimates on the total fiber intake (TFI) in the HG diet. They estimated that TFI would have averaged 150 g/day and was not likely lower than 70 g/day. This was due to the use of uncultivated vegetables and fruits, which are more fibrous (13.3 g fiber/100 g) than the commercial ones (4.2 g/100 g) [31]. Even though in most studies TFI is lower than that estimated by Konner, the current recommended daily intake is almost always achieved due to the high dietary intake of fruits and vegetables, despite the drastic reduction of cereal fibers. Konner and Eaton [3] also stated that the low amount of phytic acid, together with the high calcium intake and the net negative acid load, makes HG diet protective for low bone mineral density and fractures. An adequate calcium intake is fundamental to the prevention of osteoporosis, but habitual physical activity is equally significant [40, 41].The calcium intake in a HG diet is still an open question. The Hunter-gatherer diet is found lacking in some micronutrients, such as calcium and vitamin D. The content of Table II shows how calcium and vitamin D intake is different between the estimated intake by Konner [3] and a typical HG diet used in clinical trials [42]. This deficiency in calcium is probably due to the absence of milk, dairy farm products, cereals and legumes.

Finally, the level of physical activity was very different in the ancestral years and this positively affected bone mass and metabolism, in contrast with very different sets of conditions of the recent time.

WHAT EFFECTS DOES A PALEOLITHIC DIET HAVE?

Jönsson's study [29] was the first to show that a Paleolithic diet improves glycemic control and several cardiovascular risk factors compared to a diabetic diet in patients with T2DM. This randomized cross-over study evaluated 13 subjects with T2DM on oral agent therapy. Patients consumed, for three months each, a Paleolithic diet based on lean meat, fish, fruits, vegetables, root vegetables, eggs and nuts; and a diabetic diet designed in accordance with dietary guidelines during two consecutive three-month periods. The patients were not blinded as to which diet they were ingesting, but the investigators told them both diets were healthy and that it was unknown whether either diet was superior. Compared to the diabetic diet, the Paleolithic diet showed statistically significantly lower mean values of hemoglobin A1c, triglycerides (TG), diastolic BP, weight, BMI, and waist circumference, while mean values of HDL were higher. The larger decrease of fasting plasma glucose following the Paleolithic diet did not reach statistical significance, and systolic BP also tended to reduce following the Paleolithic diet. Ingestion of a Paleolithic diet (always compared to a diabetic diet) did not result in a significant reduction in the area under the curve between 0 and 120 min for glucose during a 75 g oral glucose tolerance test, which was a pre-specified endpoint. The impact of this study was limited by its small size.

The metabolic effects on humans consuming a Paleolithic diet have been shown in only a handful of studies to date. Jönsonn et al. [29] showed that, over a three-month study period, a Paleolithic diet improved glycemic control and several cardiovascular risk factors compared to a diabetic diet in patients with T2DM.

Spreadbury [43] reported that a diet of grain-free whole foods coupled with carbohydrate from cellular tubers, leaves,

and fruits produces a gastrointestinal microbiota consistent with our evolutionary condition, potentially explaining the exceptional macro-nutrient-independent metabolic health of non-Westernized populations, and the apparent efficacy of the modern "Paleolithic diet on satiety and metabolism". Jönsonn et al. [44] recently reported in a randomized cross-over study that a Paleolithic diet is more satiating per calorie than a diabetic diet in patients with T2DM. The Paleolithic diet was seen as instrumental to successful weight loss, albeit burdened by difficulties to adhere to. Osterdahl et al. [45] assessed the effect of a Paleolithic diet on 14 healthy volunteers during a three-week pilot study. Complete dietary assessment was available for only six subjects. They found significant improvements in weight, BMI, waist circumference, systolic BP, and Plasminogen Activator Inhibitor-1 (PAI-1). In a metabolically controlled outpatient study of nine non-obese sedentary healthy volunteers, Frassetto et al. [46] reported no daily weight loss. Participants consuming their usual diet with those under a Paleolithic type diet were compared. The participants consumed their usual diet for 3 days, three ramp-up diets of increased potassium and fiber for 7 days, then a Paleolithic type diet comprising lean meat, fruits, vegetables and nuts, and excluding non Paleolithic type foods, such as cereal grains, dairy or legumes, for 10 days. The authors concluded that even short-term consumption of a Paleolithic type diet improves BP, increases insulin sensitivity, and improves lipid profiles.

THE IMPORTANCE OF LOWERING LIPID CONCENTRATIONS IN NAFLD/NASH

NAFLD identifies the spectrum of liver disorders ranging from simple steatosis to various degree of inflammatory activity and fibrosis, configuring Non Alcoholic SteatoHepatitis (NASH).

Up to date there have been several attempts to cure NAFLD by a pharmacological approach. Among others, some studies have showed the potential efficacy of vitamin E in the treatment of NASH [47, 48]. Recently, Au et al. showed that the S-adenosyl-l-methionine and silybin combination inhibits both inflammation and oxidative stress [49]. Nevertheless, the actual view for NAFLD treatment is principally directed toward correction of the risk factors. Another attempt is based on adiponectin and its agonists, which, together with lifestyle modifications, could attenuate liver inflammation and fibrosis [50].

Reduced TG synthesis in the liver is a potential and interesting target for the treatment of NAFLD. Fernandez Giannotti et al. recently showed that diet-induced fatty liver is associated with the down-regulation of hepatic stearoyl-CoA desaturase-1 transcript and de-dimerization of the protein, and these changes were not much altered by the status of peripheral insulin resistance [51].

Insulin resistance, as frequently stressed, is usually thought to play a central role in the development of both NAFLD and NASH [52–55]. At the same time, the elevated concentrations of both glucose and free fatty acids (FFAs) in the blood contribute to excessive accumulation of neutral lipids in the liver. Donnelly et al. [55] reported that in NAFLD patients plasma FFAs were the primary contributor to the liver triacylglycerol content in the fasted state (50–70% of total FAs) and to the lipoprotein TG content in both the fed and the fasted state (50–75% of total FAs). The major part of the plasma FFAs derived from adipose tissue, which constituted 70–90% of FAs during fasting and 50–70% in the fed state. The neo-synthesis of FAs from glucose, fructose, and amino acids was also not regulated in NAFLD patients. *De novo* lipogenesis was increased in the fasting state, accounting for 25% of liver and VLDL TG compared with 5% in healthy individuals [56], and failed to elevate post-prandially. Furthermore, this study reported that there were probably two distinct pools of FAs in the liver, which were handled differently. Plasma FFAs, representing principally adipose-derived FAs, were thought to be part of a fast turnover pool that was usually incorporated into VLDLs, whereas FAs synthesized *de novo* were thought to enter a hepatic holding pool. Specifically, in the presence of peripheral insulin resistance, in which the flux of FAs from the adipose tissue is not suppressed by insulin and plasma, FFAs are constantly high and increased rates of lipogenesis may be a significant source of accumulated TG in the liver [56].

In healthy individuals, increased lipid concentrations in the liver lead to elevated VLDL production and secretion; nevertheless, in NAFLD patients, this elevation in fat export via VLDL may be impaired because of an insufficient apoB-100 synthesis, a rate-determining step in hepatocyte lipid export, being an important factor in the development of hepatic steatosis, a prerequisite for NASH [57]. Hypertriglyceridemia, low HDL concentrations, and small, dense LDL particles generally result from transformation in the concentration, size, or both of circulating VLDL [58], which together confer an elevated risk of CVD [59]. NAFLD, a further expression of the metabolic syndrome, is directly or indirectly implicated in the development and progression of CVD [60-66]. In the light of mitochondrial dysfunction, recently considered to be an important hit [67], a Paleolithic diet improving insulin resistance, ameliorating dyslipidemia might prevent the development of NAFLD/NASH.

FRUCTOSE CONSUMPTION AND NAFLD

Fructose is the main constituent of sugars (sucrose) and syrups (corn syrup) that are added to foods or beverages when they are processed or prepared, being sometimes up to 10% of total calorie assumption in the Western countries [68]. Fructose can be converted to glucose, mainly in the liver, where it is transformed into glucose, glycogen, lactate, and, to a lesser extent, FAs [69]. In animal models, diets containing elevated quantity of disposable fructose favor the progression of obesity, insulin resistance, T2DM, and dyslipidemia [68]. Hepatic steatosis is an early histological feature after fructose exposure, the inner mechanism of which is represented by hepatic insulin resistance [68]. A great deal of evidence, based on intervention trials in humans, suggests that fructose overfeeding (>50 g fructose, corresponding to 100 g sucrose/day) increases fasting and postprandial plasma TG concentrations that stimulate the *de novo* lipogenesis and the secretion of both very low density lipoproteins (VLDL) and TG as well as reduce VLDL-TG clearance in the liver [68]. That said, fructose intake as

high as 200 g/day decreases hepatic insulin sensitivity, and does not worsen the muscle insulin sensitivity in healthy fructose-fed volunteers, in net contrast to animal models. A likely interpretation is based on the fact that both insulin resistance and hyperglycemia advance quite exclusively when subjects are highly exposed to a sustained fructose ingestion, but only in conjunction with altered body composition [68]. In support of this hypothesis, there is a large body of evidence that fructose has no negative effects when utilized in moderate amounts [70]. A short-term fructose overfeeding has been established to provoke *de novo* lipogenesis, increasing the fat excess deposition in the liver, even though the classic feature of NAFLD in not reached [68]. As reported by Tappy et al., on the basis of longitudinal studies, a low quantity of fructose, even for a long time, does not contribute to the induction or worsening of NAFLD [68]. However, the available evidence is not sufficiently robust to draw conclusions regarding the effects of fructose on NAFLD [71].

Probably, a Paleolithic diet being low in fructose might prevent the progression of NAFLD.

NAFLD, METABOLIC SYNDROME AND HEPATOCELLULAR CARCINOMA

According to a single topic conference held by the AASLD, it was shown that up to 70% of T2DM and obese subjects exhibited various degrees of NAFLD [72]. In accordance with this statement, the occurrence of NAFLD in the absence of metabolic syndrome (MS) seems to be relatively uncommon. In a study by Marchesini et al. [73], 18% of normal weight subjects developed NAFLD. However, this percentage rose dramatically in obese and MS subjects, reaching 67%. Logistic regression analysis demonstrated that the presence of MS carried a high risk of a more severe form of NAFLD, i.e., NASH, with an OR of 3.2 after correction for sex, age, and BMI.

In the study of Fujii et al., the relationship between NAFLD/NASH, T2DM, MS and hepatocellular carcinoma (HCC) development was demonstrated in a new NASH-HCC animal model [74]. A group of healthy male mice were treated with streptozocin (STZ) and a high-fat diet (HFD) or with STZ only or no treatment, and a group of healthy female mice were treated with STZ and a HFD. The infusion of STZ early after birth led to pancreatic islet injury and to diabetes. In addition, hepatocellular injury with pathological fat accumulation, increased lipogenesis and fatty acid oxidation were induced by the HFD. In the sixth week after the onset of the study, SFD-HFD mice developed fatty liver and NASH after eight weeks. Comparing these results, the authors concluded that T2DM predisposes to HCC, but liver inflammation, NASH, and fibrosis were interrelated processes and were essential for HCC evolution.

Hepatocellular carcinoma develops in two thirds of cases against the background of chronic liver disease caused by HCV and/or HBV infections or by alcohol abuse or hemochromatosis [75, 76]. A third of HCC patients are classified as having cryptogenic cirrhosis due to the absence of these underlying diseases. To date, MS seems to be the principal noxious stimulus causing the majority of cryptogenic cirrhosis cases [77]. Moreover, recent evidence has shown that obesity and T2DM have a negative prognostic impact on the natural history of HCC. Turati et al. [78] found a high risk of developing HCC in subjects with at least one of the MS components, increasing to up to four-fold if two or more factors were present. Moreover, obesity increased the risk of developing HCC and HCC mortality by 2-5 times, and T2DM doubled the HCC risk independently of the presence of alcoholic liver disease, viral hepatitis, or other demographic variables. A subsequent report also found that, in patients with viral hepatitis (HCV or HBV), the simultaneous presence of obesity and T2DM multiplied this risk by 100-fold [79].

Even in the non-fibrotic liver, MS seems to be a risk factor for the development of HCC, similar to that in the cirrhotic liver. Kawada et al. [80] enrolled a total of 1,168 patients with HCC and found that HCC developed in 75% of cases with non-cirrhotic liver affected by NASH (6 of 8 NASH subjects). This result was of poor significance due to the small number of examined cases. However, in 2012 Baffy et al. [81] reported in an interesting review that from 2004 to 2011 at least 116 cases of HCC had been demonstrated in histology-confirmed NAFLD without cirrhosis. It seems that simple MS and NAFLD, in the absence of NASH, can promote the development of HCC, as shown by Guzman et al. [82].

Insulin growth factor (IGF)-1 and IGF-2 interact with specific receptors (IGF-1R and IGF-2R), as reported by Scalera et al. [83]. IGF-1R is over-expressed *in vitro* and in animal models of HCC and it was demonstrated that IGF ligands exerted their effects on HCC cells through IGF-1R and that it was involved in the degeneration of pre-neoplastic lesions via an increase in their mitotic activity [83].

Thus, convincing experimental evidence obtained from invertebrates and nonhuman vertebrates taught us that down-regulated insulin/IGF-1 signaling (IIS) is of critical importance for metabolic homeostasis, improved oxidative stress responses and longevity, as suggested by Melnik et al. [84].

The Paleolithic diet, which excludes hyperglycemic carbohydrates and insulin-tropic dairy decreasing IIS, has been successfully introduced for the prevention and treatment of T2DM, MS and CVD [46, 84].

FUTURE REMARKS

It is important to identify a safer and more effective diet to counteract obesity or T2DM and their related NAFLD [85, 86]. Similarly, it is of interest to compare the Paleolithic diet to other diets in normal-weight, overweight and obese patients. Potential risks of a Paleolithic diet include deficiencies of vitamin D and calcium as well as presentation to environmental toxins from the high intake of fish [87]. All populations seem to develop diseases of civilization that may be related to the consumption of industry-sponsored foods beyond sedentary lifestyles [88]. Groups, whose way of dietary pattern resembles a Paleolithic diet, have low rates of complex degenerative diseases due to higher insulin sensitivity, at the level of muscle and adipose tissues rather than the liver, which is central to the prevention of developing CVD [89, 90].The view of Eaton et al. is clearly explained in this paragraph, resembling the Ockham's razor, "the theory that deviation from our ancestral lifestyle elevates, while reversion toward

the basics of Stone Age existence decreases, chronic disease risk must be judged by its simplicity, intrinsic elegance, and conceptual economy" [30].

An interesting aspect of diet-induced obesity relies on gut flora-mediated epigenetic changes. The microbiota of modern man has a much reduced size and diversity in comparison to what our Paleolithic forefathers had, and individuals living a rural life have today [91]. As it is known, the transcription factor Nrf2, nuclear factor erythroid-2-related factor 2, activates the transcription of over 500 genes in the human genome, most of which have cytoprotective functions [92]. The most healthy diets known, such as the traditional Mediterranean, are rich in Nrf2 raising nutrients as apparently was the Paleolithic diet that our ancestors ate, as suggested by Pall and Levine [92]. Another group, of Stomby et al. [93], showed that a Paleolithic-type diet decreases transcript levels of 11β hydroxysteroid dehydrogenase type 1 (11βHSD1) in subcutaneous adipose tissue, influencing the pathogenesis of hepatic steatosis, in this manner clarifying the link between hypercortisolism [94] and the potential relationship between NAFLD and HG diet. Finally, earlier studies showed that the supplementation of a high-fat diet with protein, main constituents of the Paleolithic diet, can prevent and even reverse hepatic steatosis [95].

Dietary restrictions, according to the Paleolithic diet, by decreasing IIS may reduce the risk of age-related diseases. A note of caution should be added to this statement in the sense that, if the ancestral diet is rich in game and organ meats, it should be also rich in purines and maybe result in hyperuricaemia, which in the Western countries has been directly linked to insulin resistance and the MS. Finally, the meat-based food system requires more energy, land, and water resources than other diets, such as the lactoovovegetarian diet, making in this limited sense, the ancestral diet less sustainable [96].

CONCLUSION

Current dietary patterns are considered the cause of declining health, being mandatory to reduce the visceral fat [97]. Obesity and T2DM are among the major public health concerns [98]. The Paleolithic diet might be an acceptable antidote to the unhealthy Western diet, but only unequivocal results from randomized controlled trials or meta-analyses will support this hypothesis.

There is a debate around the actual food consumed by our ancestors, which varied according to places, seasons and food availability [99], and for this reason a definite and clear vision of this type of diet merits further more sophisticated studies before it is advised to be followed, also taking into account that the Paleolithic diet constituents are only supposed [100], even though with great approximation.

The current recommendations are for weight reduction by dietary modification. We believe that diets more closely resembling those of HG societies should be studied for the prevention and treatment of NAFLD and associated conditions, and that this is a matter of urgency. This is due to two orders of factors: 1) NALFD and comorbidities are highly prevalent and represent a huge personal and national burden in terms of reduced quality of life and economic burden respectively; and 2) most if not all guidelines for the prevention of and treatment of NAFLD, type 2 diabetes, obesity, and related conditions have a lifestyle, particularly the diet, as their foundation.

Conflicts of interest: None to declare.

REFERENCES

1. Boers I, Muskiet FA, Berkelaar E, et al. Favourable effects of consuming a Palaeolithic-type diet on characteristics of the metabolic syndrome: a randomized controlled pilot-study. Lipids Health Dis 2014; 13: 160. doi: 10.1186/1476-511X-13-160
2. Cordain L, Eaton SB, Miller JB, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. Eur J Clin Nutr 2002; 56: S42-S52. doi: 10.1038/sj/ejcn/1601353
3. Konner M, Eaton SB. Paleolithic nutrition: twenty-five years later. Nutr Clin Pract 2010; 25: 594-602. doi: 10.1177/0884533610385702
4. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 2005; 81: 341-354.
5. Jönsson T, Olsson S, Ahrén B, Bøg-Hansen TC, Dole A, Lindeberg S. Agrarian diet and diseases of affluence--do evolutionary novel dietary lectins cause leptin resistance? BMC Endocr Disord 2005; 5:10. doi: 10.1186/1472-6823-5-10
6. Ströhle A, Hahn A, Sebastian A. Latitude, local ecology, and hunter-gatherer dietary acid load: implications from evolutionary ecology. Am J Clin Nutr 2010; 92: 940-945. doi: 10.3945/ajcn.2010.29815
7. McKeown T. The direction of medical research. Lancet. 1979; 2: 1281-1284. doi: 10.1016/S0140-6736(79)92290-6
8. O'Dea K. Westernisation, insulin resistance and diabetes in Australian aborigines. Med J Aust 1991; 155: 258-264.
9. Lindeberg S. Paleolithic diets as a model for prevention and treatment of Western disease. Am J Hum Biol 2012; 24: 110-115. doi: 10.1002/ajhb.22218
10. Astrup A, Dyerberg J, Elwood P, et al. The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? Am J Clin Nutr 2011; 93: 684-688. doi: 10.3945/ajcn.110.004622
11. Bordone L, Guarente L. Calorie restriction, SIRT1 and metabolism: understanding longevity. Nat Rev Mol Cell Biol 2005; 6: 298-305. doi: 10.1038/nrm1616
12. Spreadbury I. Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. Diabetes Metab Syndr Obes 2012; 5: 175-189. doi: 10.2147/DMSO.S33473
13. O'Keefe JH Jr, Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome: how to become a 21st-century hunter-gatherer. Mayo Clin Proc 2004; 79: 101-108. doi: 10.4065/79.1.101
14. Farkas J, Angel A, Avigan MI. Studies on the compartmentation of lipid in adipose cells. II. Cholesterol accumulation and distribution in adipose tissue components. J Lipid Res 1973; 14: 344-356.
15. Igl W, Kamal-Eldin A, Johansson A, et al. Animal source food intake and association with blood cholesterol, glycerophospholipids and sphingolipids in a northern Swedish population. Int J Circumpolar Health 2013; 72. doi: 10.3402/ijch.v72i0.21162
16. Wolmarans P, Laubscher JA, van der Merwe S, et al. Effects of a prudent diet containing either lean beef and mutton or fish and skinless chicken on the plasma lipoproteins and fatty acid composition of triacylglycerol

and cholesteryl ester of hypercholesterolemic subjects. J Nutr Biochem 1999; 10: 598-608. PMID: 15539255
17. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. N Engl J Med. 1990 Aug 16;323(7):439-45. doi: 10.1016/S0955-2863(99)00048-0
18. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003; 77: 1146-1155.
19. Misra A, Singhal N, Khurana L. Obesity, the metabolic syndrome, and type 2 diabetes in developing countries: role of dietary fats and oils. J Am Coll Nutr 2010; 29: 289S-301S. doi: 10.1080/07315724.2010.10719844
20. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009; 360: 859-873. doi: 10.1056/NEJMoa0804748
21. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998; 280: 2001-2007. doi: 10.1001/jama.280.23.2001
22. Flock MR, Harris WS, Kris-Etherton PM. Long-chain omega-3 fatty acids: time to establish a dietary reference intake. Nutr Rev. 2013; 71: 692-707. doi: 10.1111/nure.12071
23. Kris-Etherton PM, Grieger JA, Etherton TD. Dietary reference intakes for DHA and EPA. Prostaglandins Leukot Essent Fatty Acids 2009; 81: 99-104. doi: 10.1016/j.plefa.2009.05.011
24. Borreani G, Coppa M, Revello-Chion A, et al. Effect of different feeding strategies in intensive dairy farming systems on milk fatty acid profiles, and implications on feeding costs in Italy. J Dairy Sci 2013; 96: 6840-6855. doi: 10.3168/jds.2013-6710
25. Beezhold BL, Johnston CS. Restriction of meat, fish, and poultry in omnivores improves mood: a pilot randomized controlled trial. Nutr J 2012; 11: 9. doi: 10.1186/1475-2891-11-9
26. Hunter JE, Zhang J, Kris-Etherton PM. Cardiovascular disease risk of dietary stearic acid compared with trans, other saturated, and unsaturated fatty acids: a systematic review. Am J Clin Nutr 2010; 91: 46-63. doi: 10.3945/ajcn.2009.27661
27. Cordain L, Miller JB, Eaton SB, Mann N. Macronutrient estimations in hunter-gatherer diets. Am J Clin Nutr 2000; 72: 1589-1592.
28. Daley CA, Abbott A, Doyle PS, Nader GA, Larson S. A review of fatty acid profiles and antioxidant content in grass-fed and grain-fed beef. Nutr J 2010; 9: 10. doi: 10.1186/1475-2891-9-10
29. Jönsson T, Granfeldt Y, Ahrén B, et al. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. Cardiovasc Diabetol 2009; 8: 35. doi: 10.1186/1475-2840-8-35
30. Eaton SB, Konner MJ, Cordain L. Diet-dependent acid load, Paleolithic nutrition, and evolutionary health promotion. Am J Clin Nutr 2010; 91: 295-297. doi: 10.3945/ajcn.2009.29058
31. Wylie-Rosett J, Aebersold K, Conlon B, Isasi CR, Ostrovsky NW. Health effects of low-carbohydrate diets: where should new research go? Curr Diab Rep 2013; 13: 271-278. doi: 10.1007/s11892-012-0357-5
32. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 1985; 312: 283-289. doi: 10.1056/NEJM198501313120505
33. Stamler J. The INTERSALT Study: background, methods, findings, and implications. Am J Clin Nutr 1997; 65: 626S-642S.
34. Freedman DA, Petitti DB. Salt and blood pressure. Conventional wisdom reconsidered. Eval Rev 2001; 25: 267-287. doi: 10.1177/0193841X0102500301
35. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ. 2009; 339: b4567. doi: 10.1136/bmj.b4567
36. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010; 362: 590-599. doi: 10.1056/NEJMoa0907355
37. Appel LJ, Anderson CA. Compelling evidence for public health action to reduce salt intake. N Engl J Med 2010; 362: 650-652. doi: 10.1056/NEJMe0910352
38. Eaton SB, Eaton SB 3rd, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. Eur J Clin Nutr 1997; 51: 207-216. doi: 10.1038/sj.ejcn.1600389
39. Ströhle A, Hahn A, Sebastian A. Estimation of the diet-dependent net acid load in 229 worldwide historically studied hunter-gatherer societies. Am J Clin Nutr 2010; 91: 406-412. doi: 10.3945/ajcn.2009.28637
40. Sinaki M, Pfeifer M, Preisinger E, et al. The role of exercise in the treatment of osteoporosis. Curr Osteoporos Rep 2010; 8: 138-144. doi: 10.1007/s11914-010-0019-y
41. Ruiz-Montero PJ, Castillo-Rodriguez A, Mikalački M, Nebojsa C, Korovljev D. 24-weeks Pilates-aerobic and educative training to improve body fat mass in elderly Serbian women. Clin Interv Aging 2014; 9: 243-248. doi: 10.2147/CIA.S52077
42. Jew S, AbuMweis SS, Jones PJ. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. J Med Food 2009; 12: 925-934. doi: 10.1089/jmf.2008.0268
43. Spreadbury I. Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. Diabetes Metab Syndr Obes 2012; 5: 175-189. doi: 10.2147/DMSO.S33473
44. Jönsson T, Granfeldt Y, Lindeberg S, Hallberg AC. Subjective satiety and other experiences of a Paleolithic diet compared to a diabetes diet in patients with type 2 diabetes. Nutr J 2013; 12: 105. doi: 10.1186/1475-2891-12-105
45. Österdahl M, Kocturk T, Koochek A, Wändell PE. Effects of a short-term intervention with a paleolithic diet in healthy volunteers. Eur J Clin Nutr 2008; 62: 682-685. doi: 10.1038/sj.ejcn.1602790
46. Frassetto LA, Schloetter M, Mietus-Synder M, Morris RC Jr, Sebastian A. Metabolic and physiologic improvements from consuming a paleolithic, hunter-gatherer type diet. Eur J Clin Nutr 2009; 63 : 947-955.doi: 10.1038/ejcn.2009.4
47. Erhardt A, Stahl W, Sies H, Lirussi F, Donner A, Häussinger D. Plasma levels of vitamin E and carotenoids are decreased in patients with Nonalcoholic Steatohepatitis (NASH). Eur J Med Res 2011; 16: 76-78. doi: 10.1186/2047-783X-16-2-76
48. Harrison SA, Ward JA, Schenker S. The role of vitamin E and C therapy in NASH. Am J Gastroenterol 2004; 99: 1862. doi: 10.1111/j.1572-0241.2004.40539_3.x
49. Au AY, Hasenwinkel JM, Frondoza CG. Hepatoprotective effects of S-adenosylmethionine and silybin on canine hepatocytes in vitro. J Anim Physiol Anim Nutr (Berl) 2013; 97: 331-341. doi: 10.1111/j.1439-0396.2012.01275.x
50. Finelli C, Tarantino G. What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? World J Gastroenterol 2013; 19: 802-812. doi: 10.3748/wjg.v19.i6.802
51. Fernández Gianotti T, Burgueño A, Gonzales Mansilla N, Pirola CJ, Sookoian S. Fatty liver is associated with transcriptional downregulation of stearoyl-CoA desaturase and impaired protein dimerization. PLoS One 2013; 8: e76912. doi: 10.1371/journal.pone.0076912

52. Uslusoy HS, Nak SG, Gülten M. Noninvasive predictors for liver fibrosis in patients with nonalcoholic steatohepatitis. World J Hepatol 2011; 3: 219-227. doi: 10.4254/wjh.v3.i8.219
53. Mazza A, Fruci B, Garinis GA, Giuliano S, Malaguarnera R, Belfiore A. The role of metformin in the management of NAFLD. Exp Diabetes Res 2012; 2012: 716404. doi: 10.1155/2012/716404
54. Hsieh PS, Hsieh YJ. Impact of liver diseases on the development of type 2 diabetes mellitus. World J Gastroenterol 2011; 17: 5240-5245. doi: 10.3748/wjg.v17.i48.5240
55. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 2005; 115: 1343–1351. doi: 10.1172/JCI23621
56. Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. Am J Physiol Endocrinol Metab 2010; 298: E449-466. doi: 10.1152/ajpendo.00559.2009
57. Charlton M, Sreekumar R, Rasmussen D, Lindor K, Nair KS. Apolipoprotein synthesis in nonalcoholic steatohepatitis. Hepatology 2002; 35: 898 –904. PMID: 11915037
58. Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin resistant states. Clin Chim Acta. 2006; 368: 1–19. doi: 10.1053/jhep.2002.32527
59. Assy N, Nassar F, Nasser G, Grosovski M. Olive oil consumption and non-alcoholic fatty liver disease. World J Gastroenterol 2009; 15: 1809-1815. doi: 10.3748/wjg.15.1809
60. Tarantino G, Caputi A. JNKs, insulin resistance and inflammation: A possible link between NAFLD and coronary artery disease. World J Gastroenterol 2011; 17: 3785-3794. doi: 10.3748/wjg.v17.i33.3785
61. Pacana T, Fuchs M. The cardiovascular link to non alcoholic fatty liver disease: a critical analysis. Clin Liver Dis 2012; 16: 599-613. doi: 10.1016/j.cld.2012.05.008
62. Santos RD, Agewall S. Non-alcoholic fatty liver disease and cardiovascular disease. Atherosclerosis 2012; 224: 324-325. doi: 10.1016/j.atherosclerosis.2012.07.018
63. Tarantino G, Finelli C, Colao A, et al. Are hepatic steatosis and carotid intima media thickness associated in obese patients with normal or slightly elevated gamma-glutamyl-transferase? J Transl Med 2012; 10: 50. doi: 10.1186/1479-5876-10-50
64. Tarantino G, Finelli C, Scopacasa F, et al. Circulating levels of sirtuin 4, a potential marker of oxidative metabolism, related to coronary artery disease in obese patients suffering from NAFLD, with normal or slightly increased liver enzymes. Oxid Med Cell Longev 2014; 2014: 920676. doi: 10.1155/2014/920676
65. Tarantino G, Costantini S, Finelli C, et al. Is serum Interleukin-17 associated with early atherosclerosis in obese patients? J Transl Med 2014; 12: 214. doi: 10.1186/s12967-014-0214-1
66. Tarantino G, Costantini S, Finelli C, et al. Carotid intima-media thickness is predicted by combined eotaxin levels and severity of hepatic steatosis at ultrasonography in obese patients with Nonalcoholic Fatty Liver Disease. PLoS One 2014; 9: e105610. doi: 10.1371/journal.pone.0105610
67. García-Ruiz C, Baulies A, Mari M, García-Rovés PM, Fernandez-Checa JC. Mitochondrial dysfunction in non-alcoholic fatty liver disease and insulin resistance: cause or consequence? Free Radic Res 2013; 47: 854-868. doi: 10.3109/10715762.2013.830717
68. Tappy L, Lê KA. Does fructose consumption contribute to non-alcoholic fatty liver disease? Clin Res Hepatol Gastroenterol 2012; 36: 554-560. doi: 10.1016/j.clinre.2012.06.005
69. Yilmaz Y. Review article: fructose in non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2012; 35: 1135-1144. doi: 10.1111/j.1365-2036.2012.05080.x
70. Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol 2008; 48: 993-999. doi: 10.1016/j.jhep.2008.02.011
71. Chung M, Ma J, Patel K, Berger S, Lau J, Lichtenstein AH. Fructose, high-fructose corn syrup, sucrose, and nonalcoholic fatty liver disease or indexes of liver health: a systematic review and meta-analysis. Am J Clin Nutr 2014; 100: 833-849. doi: 10.3945/ajcn.114.086314
72. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology 2003; 37: 1202-1219. doi: 10.1053/jhep.2003.50193
73. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003; 37: 917-923. doi: 10.1053/jhep.2003.50161
74. Fujii M, Shibazaki Y, Wakamatsu K, et al. A murine model for non-alcoholic steatohepatitis showing evidence of association between diabetes and hepatocellular carcinoma. Med Mol Morphol 2013; 46: 141-152 doi: 10.1007/s00795-013-0016-1
75. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004; 127: 1372-1380. doi: 10.1053/j.gastro.2004.07.020
76. Franceschi S, Raza SA. Epidemiology and prevention of hepatocellular carcinoma. Cancer Lett 2009; 286: 5-8. doi: 10.1016/j.canlet.2008.10.046
77. Davis GL, Dempster J, Meler JD, et al. Hepatocellular carcinoma: management of an increasingly common problem. Proc (Bayl Univ Med Cent) 2008; 21: 266-280.
78. Turati F, Talamini R, Pelucchi C, et al. Metabolic syndrome and hepatocellular carcinoma risk. Br J Cancer 2013; 108: 222-228. doi: 10.1038/bjc.2012.492
79. Chen CL, Yang HI, Yang WS, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterology 2008; 135: 111-121. doi: 10.1053/j.gastro.2008.03.073
80. Kawada N, Imanaka K, Kawaguchi T, et al. Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. J Gastroenterol 2009; 44: 1190-1194. doi: 10.1007/s00535-009-0112-0
81. Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol 2012; 56: 1384-1391. doi: 10.1016/j.jhep.2011.10.027
82. Guzman G, Brunt EM, Petrovic LM, Chejfec G, Layden TJ, Cotler SJ. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? Arch Pathol Lab Med 2008; 132: 1761-1766. doi: 10.1043/1543-2165-132.11.1761
83. Scalera A, Tarantino G. Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease? World J Gastroenterol 2014; 20: 9217-9228. doi: 10.3748/wjg.v20.i28.9217
84. Melnik BC, John SM, Schmitz G. Over-stimulation of insulin/IGF-1 signaling by western diet may promote diseases of civilization: lessons learnt from laron syndrome. Nutr Metab (Lond) 2011; 8: 41. doi: 10.1186/1743-7075-8-41
85. Finelli C, Tarantino G. Is there any consensus as to what diet or lifestyle approach is the right one for NAFLD patients? J Gastrointestin Liver Dis 2012; 21: 293-302.
86. Finelli C, Tarantino G. Have guidelines addressing physical activity been established in nonalcoholic fatty liver disease? World J Gastroenterol 2012; 18: 6790–6800. doi: 10.3748/wjg.v18.i46.6790

87. Jew S, AbuMweis SS, Jones PJ. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. J Med Food 2009; 12: 925-934. doi: 10.1089/jmf.2008.0268
88. Milton K. The critical role played by animal source foods in human (Homo) evolution. J Nutr 2003; 133: 3886S-3892S.
89. Kanat M, Norton L, Winnier D, Jenkinson C, DeFronzo RA, Abdul-Ghani MA. Impaired early- but not late-phase insulin secretion in subjects with impaired fasting glucose. Acta Diabetol 2011; 48: 209-217. doi: 10.1007/s00592-011-0285-x
90. Muskiet FA, Carrera-Bastos P. Beyond the Paleolithic prescription: Commentary. Nutr Rev 2014; 72: 285-286. doi: 10.1111/nure.12112
91. Bengmark S. Nutrition of the critically ill - emphasis on liver and pancreas. Hepatobiliary Surg Nutr 2012; 1: 25-52. doi: 10.3978/j.issn.2304-3881.2012.10.14
92. Pall ML, Levine S. Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. Sheng Li Xue Bao 2015; 67: 1-18. doi: 10.13294/j.aps.2015.0001
93. Stomby A, Simonyte K, Mellberg C, et al. Diet-induced weight loss has chronic tissue-specific effects on glucocorticoid metabolism in overweight postmenopausal women. Int J Obes (Lond) 2015; 39: 814-819. doi: 10.1038/ijo.2014.188
94. Tarantino G, Finelli C. Pathogenesis of hepatic steatosis: the link between hypercortisolism and non-alcoholic fatty liver disease. World J Gastroenterol 2013; 19: 6735-6743. doi: 10.3748/wjg.v19.i40.6735
95. Kuipers RS, Joordens JC, Muskiet FA. A multidisciplinary reconstruction of Palaeolithic nutrition that holds promise for the prevention and treatment of diseases of civilisation. Nutr Res Rev 2012; 25: 96-129. doi: 10.1017/S0954422412000017
96. Pimentel D, Pimentel M. Sustainability of meat-based and plant-based diets and the environment. Am J Clin Nutr 2003; 78(3 Suppl): 660S-663S.
97. Finelli C, Sommella L, Gioia S, La Sala N, Tarantino G. Should visceral fat be reduced to increase longevity? Ageing Res Rev 2013; 12: 996-1004. doi: 10.1016/j.arr.2013.05.007
98. O'Rahilly S. Human genetics illuminates the paths to metabolic disease. Nature 2009; 462: 307-314. doi: 10.1038/nature08532
99. Garcia-Caraballo SC, Comhair TM, Verheyen F, et al. Prevention and reversal of hepatic steatosis with a high-protein diet in mice. Biochim Biophys Acta 2013; 1832: 685-695. doi: 10.1016/j.bbadis.2013.02.003
100. Murdock GP. Ethnographic atlas: a summary. Ethnology 1967; 6:109–236. doi: 10.2307/3772751