



Liver fattening during feast and famine: An evolutionary paradox

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Summary Liver disease is one of the features of metabolic syndrome, one of the most occurring diseases of the twenty-first century. During food deprivation and starvation, adipose tissue elsewhere in the body delivers lipid components to the liver where they are stored as triacylglycerols (TG). Continuous and excessive food intake, on the other hand, leads to liver fattening (hepatic steatosis). In the long term this reaction is pathogenic mainly by inflammation reactions. We postulate the hypothesis in the evolutionary context that individuals with genes promoting the efficient deposition of fat during periods between famines (thrifty genes) in combination with a proinflammatory genotype would be favored and be selected during the course of evolution. Furthermore we postulate the hypothesis that the majority of man, living in a world where famine never comes, are physiologically not adapted to modern social behavior with abundance of food.

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Introduction, hepatic steatosis

Hepatic steatosis, or the presence of significant amounts of triacylglycerol (TG) in hepatocytes, was long thought to be mainly a symptom of alcoholic liver disease. In recent years, however, steatosis has been found in the absence of alcohol abuse and led to the definition of a series of disorders ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) [1].

There is now convincing evidence that nonalcoholic fatty liver disease (NAFLD) is a component of the metabolic syndrome [2]. Metabolic syndrome (obesity) affects about 20% of the popula-

tion [3] and its prevalence is strongly increasing due to changes in life style and diet [4], combined with genetic susceptibility [5]. It is a strong risk factor for the development of type 2 diabetes, premature atherosclerosis, and stroke [6] and represents a major health threat to society as a whole. Despite the magnitude of the problem, surprisingly little is known of the etiology connecting the different symptoms of metabolic syndrome (e.g. hepatic steatosis) with each other and with type 2 diabetes and premature atherosclerosis. A striking contribution of both environmental and genetic factors has been shown in both animal [7] and human studies [6].

Nonalcoholic fatty liver disease, the major reason for abnormal liver function in the Western world, is associated with obesity and diabetes and

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is characterized by insulin resistance (IR). The exact mechanism is unclear but in general Hepatic steatosis may progress to steatohepatitis, which leads to fibrosis and cirrhosis. This progression may be due to damage caused by lipid peroxidation and the production of reactive oxygen species leading to IR [8]. IR is regulated by mediators from cells of the immune system or adipocytes and proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF α) [9]. As a paradox hepatic steatosis (TG-accumulation) has recently also been demonstrated with modern LCMS techniques in a mouse model of 24 h of starvation [10].

Since in chronic liver disease (CLD), numerous aetiological, environmental, nutritional and metabolic factors are involved, and the term CLD embraces different stages of liver dysfunction the pathogenic mechanisms underlying the relationship between IR or diabetes and CLD remain to be elucidated [11]. In this manuscript we hypothesize that hepatic steatosis has an evolutionary cause.

From steatosis to steatohepatitis, the two hit model

NAFLD is commonly associated with obesity, diabetes mellitus, and hypertriglyceridemia; elements of the metabolic syndrome [12]. The "two-hit" hypothesis is the leading theory of the pathogenesis of nonalcoholic steatohepatitis. It is described in [12]. In this theory, the "first hit" is that hepatic steatosis causes insulin resistance. A state of insulin resistance frequently develops during acute or prolonged stress or other situations such as famine or obesity or inflammation [13]. In the hypothesis insulin resistance is believed to lead to the accumulation of triacylglycerols in hepatocytes. Excessive fat in the hepatocytes may set the stage for the fibrosis and necroinflammation by an increase in oxidative stress (reactive oxygen species) or cytokine production [12] (Fig. 1).

The second hit is characterized by Cytokines, fatty acids and oxidative stress [12] (Fig. 1). Reactive oxygen species can induce liver injury by interacting with biomolecules (e.g., lipids, proteins, and nucleic acids), altering their structure and, as a consequence, their function. A potential source of reactive oxygen species in non-alcoholic steatohepatitis are the mitochondria. One can think of different interactions between dysregulation of fat metabolism and mitochondrial dysfunction in the hepatocyte in non-alcoholic steatohepatitis. These mechanisms can be impaired fatty acid oxidation, increased fatty acid synthesis from glucose

Pathogenesis of NAFLD: The 'multiple-hit' hypothesis

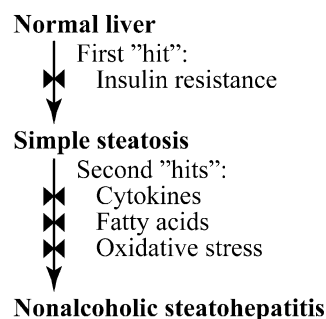


Figure 1 The 'multiple hit' hypothesis of Collantes et al. [12]. In this theory, the "first hit" is that hepatic steatosis causes insulin resistance. In the hypothesis insulin resistance is believed to lead to the accumulation of triacylglycerols in hepatocytes. Excessive fat in the hepatocytes may lead to the "second hit", fibrosis and necroinflammation by an increase in oxidative stress (reactive oxygen species) or cytokine production. These can induce liver injury by interacting with biomolecules (e.g., lipids, proteins, and nucleic acids), altering their structure and, as a consequence, their function.

or hepatic triglyceride accumulation [14]. Human beings with non-alcoholic steatohepatitis have increased serum concentrations of TNF- α and hepatic TNF- α as one mechanism for liver injury [14]. Also the largest number of activated genes in obesity (white adipose) are inflammatory genes, most of which are from macrophages [13].

Liver fattening in the evolutionary context

Hunter-gatherer with thrifty genes

Conditions for early man in the Late Paleolithic pre-agricultural hunter-gatherer society (35.000–20.000 before Christ) suggest periods of insufficient food intake punctuated by the irregular bounty of the kill. The concept of cycles of feast and famine engendered Neel's [15] 'thrifty gene' hypothesis. This concept implies the mechanism of the cycling of metabolic processes with the fluxes in feast and famine. During periods of feast individuals with thrifty metabolic processes would store more food calories as fat. On the other hand, during periods of food shortage, there is a gradual shift in whole-body fuel utilization from carbohydrates and fat in the fed state to almost exclusively fat starting already after one day of fasting. When glucose availability is low during periods of starvation, the triacylglycerols (TG) stored in adipose tissue are hydrolyzed to free fatty acids (FFA) and mobi-

lized into plasma to reach the liver where they play a major role in energy production [16]. The liver plays a central and pivotal role in these energy conversions and is the major sink of fatty acids in the form of TG. From here on energy stores in the form of ketone bodies are released to supply vital organs like brain, heart and muscle with sufficient energy.

Insulin resistance in evolution, the “proinflammatory” genotype

Fernández-Real and Ricart [17] introduced a unifying hypothesis of the relation between insulin resistance and inflammatory response in the development of diabetes. For our ancestors in the era of the hunter-gatherer lifestyle, the risk of injury was high and periods of famine were frequent. The hypothesis is that inflammation could be intrinsic to insulin resistance and Type 2 diabetes mellitus and that beneficial conditions determine the beneficial or adverse effect of a “proinflammatory” genotype.

It would be best to select those genes that imply the best defence against infection and trauma with minimal caloric intake. For our ancestors, a high cytokine responder or moderate insulin resistance genotype was advantageous. At first, an accidental injury is successfully eradicated, because the inflammatory effect is not inhibited by insulin and cytokine levels are elevated. And secondly, by inducing muscle insulin resistance, energetic substrates are safeguarded for brain metabolism in periods of famine [17].

In the presence of an insulin resistance genotype and high carbohydrate diet, increased saturated fat, low fibre and sedentary habit, a high cytokine responder genotype would be prone to deterioration of insulin resistance and, finally to Type 2 diabetes mellitus [17].

Hypothesis

In this manuscript we postulate the hypothesis that the survival strategy of TG accumulation in the liver under conditions of starvation is at first beneficial but in stages of food abundance is detrimental to the organism. Furthermore we postulate that long term exposure of the liver to abundance of food may switch from a benign survival strategys (hepatic steatosis) to pathogenesis via the “first hit” to insulin resistance and via the “second hit” to inflammation, cell death and fibrosis (steatohepatitis). This is earlier described in this manuscript by the two hit model [12] (Fig. 1).

We postulate the hypothesis that during the course of evolution a selection is made for individuals with thrifty genes [15] and a selection for a high cytokine responder. Both selection mechanisms are nowadays disadvantageous resulting in obese individuals due to thrifty genes and IR individuals due to a high inflammation response.

Furthermore we hypothesize that liver injury may result in the end in a disruption of homeostasis of the organism because metabolic flux needed for proper functioning cannot be maintained. Finally we make the suggestion that part of the human population suffering from obesity and metabolic syndrome (dyslipidemia, insulin resistance, type 2 diabetes mellitus) can be explained by this mechanism of liver injury.

Discussion

Change from preagricultural hunter-gatherer society into a sedentary, food-abundant society

The concept that genetically determined capacities, which are favorable during hunter-gatherer existence, may be detrimental under conditions of abundance became clear after studying insulin resistance of the muscle [18].

Still the discussion is open. Recently, Speakman [19] gave in his review five fundamental flaws in the famine hypothesis: (1) In essence, famines are a relatively modern phenomenon and occur only about once every 100–150 years. (2) Consequently, most human populations have only experienced at most 100 famine events in their evolutionary history. (3) Famines involve increases in total mortality that only rarely exceed 10% of the population. (4) Moreover, most people in famines die of disease rather than starvation and the age distribution of mortality during famine would not result in differential mortality between lean and obese individuals. (5) A simple genetic model shows that famines provide insufficient selective advantage over an insufficient time period for a thrifty gene to have any penetration in the modern human population [19].

However there are also other studies demonstrating the contrary that fluctuations in our food supply (feast and famine) result only in a few generations in cardio-vascular disease and diabetes.

In the study of Kaati et al. [20], investigating historical data in families of an isolated parish village in North-Sweden the researchers found that seasonal overfeeding has transgenerational effects

resulting in cardio-vascular disease and diabetes in the descendants of the second or third generation [20]. In another study it was demonstrated that these aspects can also become transgenerational via the male line depending if food abundance occurs during the prepubertal period [21]. This implies a new insight in the interplay between inheritance and environment in health and development.

Liver disease in our modern society

Our society changed from a preagricultural hunter-gatherer society into a sedentary, food-abundant society whose appearance as a culture is less than 200 years old [22]. Changed environmental factors like physical inactivity, abundance of food, excessive caloric consumption and excess weight are common causal factors for chronic health conditions afflicting individuals in modern Western Society. Characteristic for these diseases is that they are slow in progression and long in continuance. Environmental factors are thought to exert their influence by altering the expression of genes that result in a phenotype that passes a threshold of biological significance with as consequence a pathogenesis [23].

In the USA nonalcoholic fatty liver disease (NAFLD) affects approximately 30 million people [24]. The accumulation of lipid in droplets in the liver that may grow in size to a significant fraction of the cytoplasmic volume is the mechanism resulting in liver disease and ‘hepatic steatosis’. The lack of a physiological limit on this accumulation may seem an unsound evolutionary strategy which is at this moment running [1]. According to Darwinian thought phenotypes with an unfavorable fat metabolism of the liver are nowadays randomly eliminated [23].

Future perspectives

Selection pressure on the phenotype, however, is not a solution to the immediate problem because this is a huge problem affecting 1.5 billion people. The real pressure is on scientists and society to find a solution for patients.

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