Journal of
Gastroenterology and Hepatology Research

ORIGINAL ARTICLE

Hints for Therapeutic Interventions Through Exploring the Effects of Calorie Restriction on NAFLD by Mechanistic Approach

Nazanin Asghari Hanjani, Mohammad Reza Vafa, Ph.D., MSPH

Nazanin Asghari Hanjani, Mohammad Reza Vafa, School of Public Health, Iran University of Medical Sciences, Iran

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Correspondence to: Mohammad Reza Vafa, Professor of Nutritional Sciences, School of Public Health, Iran University of Medical Sciences, Iran
Email: rezavafa@yahoo.com
Telephone: +98-21-86704743
Fax: +98-91-25332628

ABSTRACT

BACKGROUND: The worldwide prevalence and severity of nonalcoholic fatty liver disease are increasing in parallel with the growing obesity epidemic. According to the US Practice Guidelines for the Diagnosis and Management of NAFLD, weight loss interventions based on hypocaloric diets – either alone or in conjugation with physical activity – can reduce hepatic steatosis. Hence, understanding the ways in which calorie restriction affects NAFLD can help in developing optimal treatments.

METHOD: In this review study, the main focus was on possibly disturbed pathways in NAFLD, and how calorie restriction may attenuate them. For this purpose, both human and animal studies available through Pubmed were reviewed.

RESULTS: Calorie restriction can upregulate energy-sensing pathways, including AMPK/SIRTUIN, and downregulate insulin-signaling pathway IGF1/PI3K/AKT. In NAFLD, AKT is over-activated through the PI3K-active mTOR and FOXO recruitment. Consequences include gluconeogenic and lipogenic enzyme alteration, insulin resistance, autophagy reduction, and liver cells apoptosis, all of which may be inverted through calorie restriction. Moreover, increased mitochondrial biogenesis, reduced inflammation, and increased fatty acid oxidation are mediated through AMPK, SIRTUIN, and PPARS, all of which are altered in NAFLD.

CONCLUSION: This review outlines prominent pathways, the targeting of which may be promising for NAFLD treatment, according to evidence-based studies.

Key words: Nonalcoholic fatty liver diseases; Calorie restriction; Mechanism Insulin signaling

INTRODUCTION

Obesity and overweight prevalence are rapidly increasing globally, and are associated with dyslipidemia, reduced high-density lipoprotein (HDL), insulin resistance, NAFLD and many other metabolic disorders[1,2]. Nonalcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver in the absence of significant alcohol consumption. Originally, it was recognized in obese women with diabetes who self-reported no alcohol consumption, but whose hepatic pathological analyses showed similar features to alcoholic hepatitis[3]. In terms of epidemiology, the incidence of NAFLD is about 5-18% in Asia and 20-30% in western countries with a linear rise with diabetes and metabolic syndrome[4]. Studies suggest that there is a bilateral relationship between NAFLD and metabolic syndrome[5]. NAFLD includes a wide spectrum of conditions, spanning hepatic steatosis to more severe conditions such as steatohepatitis, cirrhosis and hepatocellular carcinoma[6]. Studies suggest the role of

genetic polymorphism on the predisposition to NAFLD. It is possible that SNAPs involved in inadequate mitochondria overload in the presence of excess fatty acid and play a role in excessive fatty acid oxidation. On the other hand, polymorphism in superoxide dismutase renders the organism ability to reduce oxidative stress. Mounting evidence point to the role of TNF in inflammatory condition and chronic disease. In this regard, TNF polymorphisms influence the vulnerability of the organism to NAFLD and the progression to a later stage[7]. Excessive intake of high glycemic carbohydrates and saturated fatty acids, which is more common in the modern, industrialized world, is associated with the development of metabolic syndrome and the accumulation of excess fatty acids in the liver; this intake is an important predictor for NAFLD[8]. Evidence suggests that whenever free fatty acid availability exceeds hepatic disposal via secretion and oxidation, it will be stored in the liver in triglyceride form. This storage mechanism can change up to sevenfold within a few hours, so it can be suggested that decreases in exogenous free fatty acid by calorie restriction can preferentially remove hepatic fat (rather than abdominal or subcutaneous fat)[9].

Calorie restriction[10] is the major form of dietary restriction, and means reducing calorie intake by about 15-40% while maintaining sufficient amounts of essential nutrients, vitamins, and minerals[11-13]. For the first time in 1913, Osborne *et al* reported that decreasing food intake in rats resulted in an increased lifespan[14]. Since then, much money and effort have been dedicated to these kind of studies, with the majority suggesting that calorie restriction is the most robust form of intervention, one which can extend lifespan and reduce age-associated diseases[12,15,16]. According to the US Practice Guideline for the Diagnosis and Management of NAFLD and other scientific societies interventions which lead to weight loss, either by hypocaloric di*et al*one or in conjugation with physical activity, can reduce hepatic steatosis[17-19]. This review gives an overview of the mechanisms of calorie restriction in NAFLD, and it tries to highlight the most important and effective pathways. Since CR is one of the most effective interventions for treating NAFLD, it is postulated that recognizing the mechanisms involved provides accurate knowledge in finding the most effective bioactive or pharmacological interventions.

METHODS

Data were obtained from original and review articles regarding the mechanical effects of CR on NAFLD. These included both human and animal studies, indexed in the PubMed online database until 2018, with the most relevant being included in the current review. The following keywords and medical subjects were searched: CR, mechanism, NAFLD, Steatohepatitis, insulin resistance, and insulin signaling. Then, we selected the most relevant full texts and reviewed the articles. Full article of relevant abstracts were reviewed thoroughly and their eligibility were re-evaluated again. Review of articles was restricted to those published in English.

RESULTS

Pathogenesis of NAFLD

Over-nutrition, under-activity, genetic factors and insulin resistance, redox imbalance, are the main reasons for NAFLD[20]. Obesity leads to disturbed nutritional management, and excess nutrients both at the cellular and the organism level. The organism cannot adapt to this challenge, and eventually, inflammation and oxidative stress occur. Increasing the level of long-chain fatty acids and their active metabolites, along with the formation of advanced glycation end-products, are thought to be important etiologic agents in the development of hyperlipidemia, inflammation, oxidative stress, insulin resistance, and hepatic steatosis[16].

In more detail, the mechanisms involved in the initiation and progression of NAFLD include the accumulation of excess fat in hepatocytes (lipotoxicity), mitochondrial damage and subsequently lower capacity of this organelle in beta-oxidation, as well as sustained endoplasmic reticulum stress; all of this is followed by oxidative stress, inflammation and cellular damage and apoptosis[21-23]. From the cell perspective, Endoplasmic reticulum stress and death receptor, activate apoptotic machinery and lead to lipotoxicity-induced hepatocyte cell death which is potentiated by enhanced fatty acid uptake due to increased fatty acid transporter proteins., kuppffer cells engulf the apoptotic hepatocyte, and then this activated kupffer cells in parallel to activated stellate cells by apoptotic bodies or TGFβ lead to severe inflammation[24]. What follows is a discussion of the most important mechanisms and their interactions with CR and NAFLD (Figure 1).

1. Insulin Resistance

Insulin resistance (IR) is a condition whereby normal insulin concentration levels cannot achieve normal responses, and higher levels are needed for normal metabolic responses in the liver which can be assessed by HOMA-IR: Homeostasis Model Assessment of Insulin Resistance[25]. Patients with NAFLD are insulin-resistant at the levels of liver, muscle and adipose tissue. These are determined by increased hepatic gluconeogenesis, reduced glucose uptake and increased free fatty acids, respectively. These phenomenon are associated with liver damage[26,27].

Insulin autophosphorylates its receptor, which leads to insulin receptor substrate (IRS1,2), tyrosine kinase, cascade activation and the translocation of the glucose transporter from cytosol to the cell membrane. Any defect in this pathway leads to a problem in glucose metabolism and IR. Based on this, serine phosphorylation of IRS occurs instead of tyrosine phosphorylation, with phosphatidylinositide-3-kinase (PI3K), JNK, AKT and glycogen synthase hindering tyrosine phosphorylation, and sometimes inducing insulin resistance[28,29].

On the other hand, increased lipogenesis, lipolysis and intake of dietary fat lead to elevated levels of free fatty acids, which translocate the PKCθ isoform to the cell membrane. The result is defective or overactivated IRS-associated-PI3K activity, which eventually leads to reduced glucose transport in muscular, hepatic and adipose tissue, as well as glycogen synthase and lipogenesis[26,30,31].

The PI3K in the insulin signaling pathway is involved in metabolism regulation, cell growth and survival. PI3K/AKT and mitogen-activated protein kinase (MAPK) signaling cascade overactivation can lead to inflammation, cell growth and mitogenesis. Moreover, AKT promotes lipogenesis by increasing SREBP1. These pathways can be inverted by CR as well[32,33]. Data suggests that CR can suppress the activation of MAPK activity and reduce inflammation. On the other hand, PI3K generates phosphatidylinositol triphosphate (PIP3), which activate 3-phosphoinositide-dependent protein kinase 1 (PDK1), PDK2 and AKT [PKB]. Genetic analyses in C.elegans and human endothelial cells demonstrated that AKT over-activation negatively regulates lifespan. CR reduces AKT activity through activating FOXO and regulating cellular reactive oxygen species[32,34-37].

1.2 FOXO

The forkhead transcription factor (FOXO) family regulates the expression of the series of target genes by direct binding to gene promoters involved in stress resistance, metabolism, cell growth and
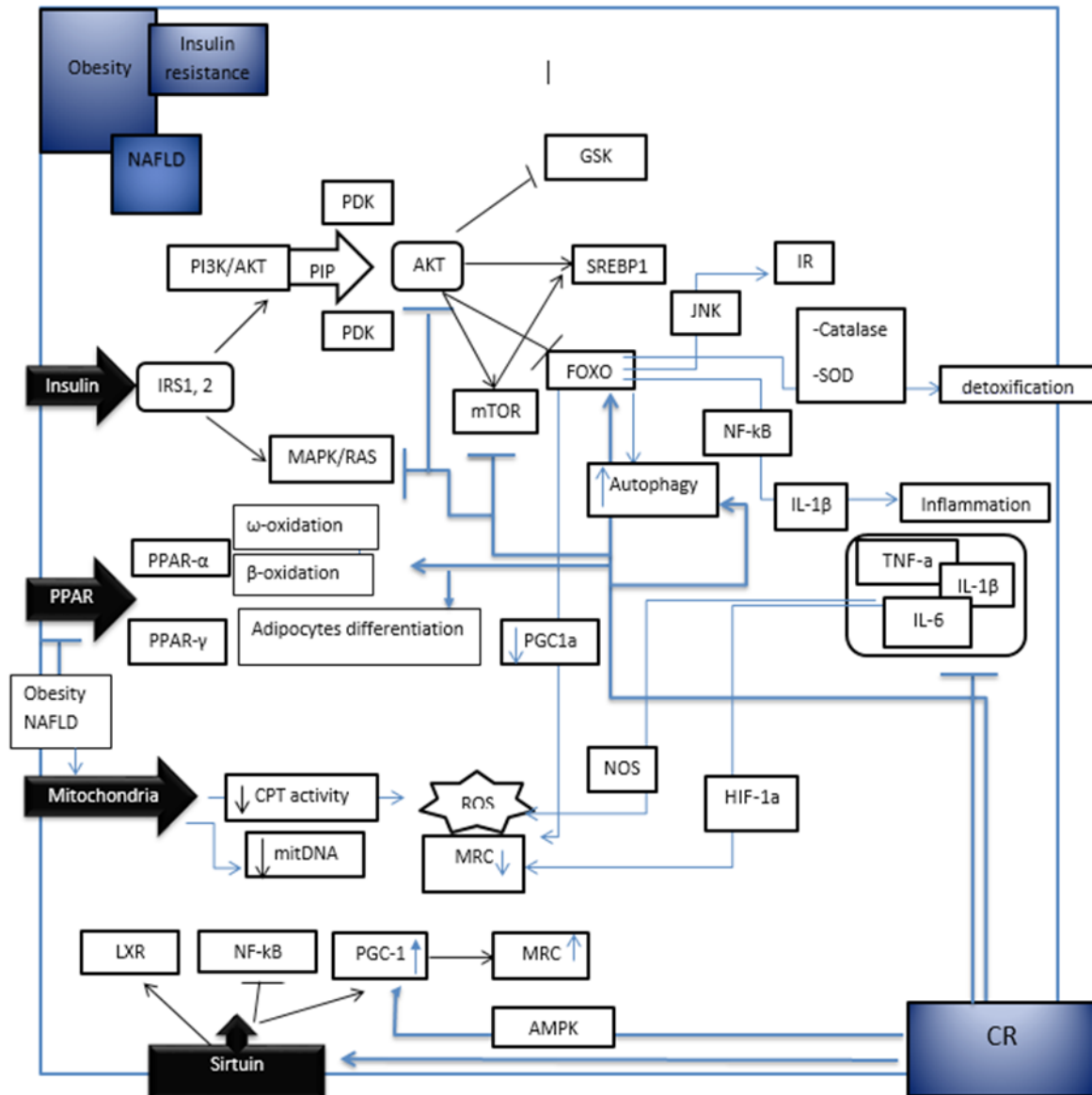
Figure 1 NOS: Nitric oxide synthases, PI3K: phosphatidylinositide-3-kinase, AKT: Protein kinase B (PKB), also known as Akt, MRC: mitochondrial respiratory chain, LXR: liver X receptor, IR: insulin resistance, CPT: carnitine palmitoyltransferase, SOD: Superoxide dismutase, HIF-α: Hypoxia-inducible factor 1-alpha. SREBP: Sterol regulatory element-binding protein. Induce: ⟶ Inhibit: ——⊣, increase: ↑, decrease: ↓

cell proliferation[38]. Increased FOXO1 mRNA resistant to insulin/IGF-1-mediated inactivation has been observed in the mouse model of insulin resistance, and in humans was associated with increased liver glucose output. Moreover, as mentioned above, JNK acts as a serine kinase and induces insulin resistance, which interacts with and is activated through FOXO1. Reduced FOXO1 expression is hypothesized to reduce hepatic gluconeogenesis and improve hepatic insulin action in parallel with enhancing peripheral insulin-stimulated glucose metabolism[39,40]. In addition, it is postulated that FOXO1 and the subunit of nuclear factor kb (NF-Kb) synergically increase macrophage production of IL-1β, but not IL-6, TNFα, and IFN-γ, while also inducing inflammation[41]. Recent data suggests that the reduction of *Drosophila* TOR activity can block the activation of dFOXO-mediated insulin resistance and metabolic syndrome phenotypes[42]. However, it is evident that activating dFOXO in *Drosophila* muscles can promote the autophagy-dependent removal of aggregated protein with muscle aging, and decrease feeding behavior and insulin production, similar to fasting[38]. Additionally, FOXO can activate detoxifying enzymes, such as catalase and

superoxide Dismutase2, hence reducing oxidative stress[43]. As mentioned above, FOXO1 plays a crucial role in regulating the proliferation and differentiation of hepatic stellate cells (HSCs) in the liver. Hypatocyte injury initiate hepatic fibrosis which is followed by HSCs activation. HSCs transdierentiates to a proliferative myofibroblast, leading to collagen deposition and fibrosis. FOXO are able to inhibit HSCs activation and increasing their apoptosis as a result of fibrogenic stimulus. Hyperinsulinemia inactivates FOXO1 through AKT, resulting in fibrosis and liver disease[44,45]. The role of FOXO on lypolisis is controversial as well. Trygelicerids synthethise increment and reduced fat oxidation in the liver are observed in FOXO overexpression. On the other hand, FOXO reduce lipogenesis through reduction of SREBP1 (an important transcription factor which regulate lipogenesis)[46]. CR activates FOXO through SIRT1 and deactivates mTOR. Therefore, the exact outcome regarding FOXO on the fatty liver cannot be precisely determined, but it is possible to say that CR can deactivate the overexpression of FOXO-mediated insulin resistance through reducing mTOR, and improve oxidative stress via the detoxifying enzyme.

1.3 Inflammation

Sedentary lifestyles, along with excessive calorie intake, not only leads to insulin resistance but also promotes obesity. During fat mass expansion and obesity, adipokines profiles change to inflammatory patterns, which occur in insulin resistance and NAFLD. Since there is a correlation between obesity, insulin resistance, NAFLD and inflammation, it is important to investigate this subject[47].

It has been reported that TNFα and IL6 play a central role in liver inflammation and consequent tumorigenesis. Uysal *et al* reported that mice without TNFα or TNFα receptors have better insulin sensitivity[48,49]. In the absence of either IL-6 or TNF receptor 1 (TNFR1), the infiltration of macrophages and neutrophils is reduced, accompanied with decreased high-fat diet-induced liver lipid accumulation and liver inflammation[50].

The production of IL-6, as a pro-inflammatory cytokine in abdominal adipose tissue, is three times higher compared with subcutaneous adipose tissue, which can potentially contribute to hepatic IR. The administration of IL-6 antibodies with an obesity-induced diet increased insulin sensitivity in mice[51,52]. Conversely, some studies suggest that IL-6 improves fatty acid oxidation through activating AMPK, which is one of the mediators of CR[53]. Generally, studies have suggested that CR can reduce inflammation through inflammatory signaling in an wide veriety of tissues, and that a 30% calorie restriction in diabetic mice could significantly lower pro-inflammatory cytokines including IL-1β, IL-4 and IL-6[54]. In a review, Jianping Ye *et al* suggested that inflammation is the consequence of the body's effort to get rid of excess energy, and similarly, calorie restriction can reverse this effect[55,56].

2. Autophagy

Synthesizing and assembling the cell components when needed, or degrading these components when they are damaged or old, is necessary for maintaining cellular hemostasis If degradation does not work properly, the cell may become cancerous or die[57].

Autophagy regulates intracellular lipid stores beside cytosolic lipase, through a process called micropexophagy. Autolipophagosome vesicles trap lipid droplets and transport them to the lysosome. The presence of this degradative lipid alternative in hepatocytes can improve their ability to mobilize lipids despite their low level of lipase in comparison to adipocytes[58]. The efficiency of the microlipophagy depends on nutritional status. A short-term increase in lipid availability leads to higher level of microautophagy, but sustained increase in lipid availability results in decreased levels of autophagy[59-61]. The major regulator of autophagy in hepatocytes, as discussed by Blommaart *et al*, is the Mammalian Target of Rapamycin (mTOR) signaling pathway[62]. Insulin activates mTOR, and the activation of this pathway leads to autophagy decline. Several mechanisms may account for this decline. Activation of AKT through PI3K prevents the formation of the TSC1/2 complex, then its downstream, Rheb protein (in its GTP-form), binds and activates mTOR[63]. TOR inhibition and AMPK activation due to calorie restriction can activate the autophagy-promoting Unc-51 like autophagy activating kinase 1 [ULK1] complex in parallel with the acetyltransferase MEC-17, which stimulates the microtubule transport machinery that is necessary for autophagy[64]. CR can down-regulate the insulin/IGF pathway (PI3K/Akt/mTOR) in parallel with upregulating energy-sensing pathways [SIRT and AMPK], which are accompanied by the overactivation of autophagy and DNA repair gene. Recent data found that Sirt activation decrease inflammation through autophagy activation from mTOR/AKT inhibition[65]. In particular, Shen chen *et al*, recently reported that nicotinamid can prevent palmitoate-induced lipotoxicityin hepatocytes through Sirt-induction of authopagy[43,66,67].

3. Mitochondrial Function

Increased level of reactive oxygen species (ROS) due to mitochondrial dysfunction is one of the well-known topics that is discussed in different studies as a key point in initiation and progression of diseases. In this regard it has been recently recognized that mitochondrial dysfunction may play a critical role in the development of NAFLD and progression to NASH[68].

Recent studies suggest that total fatty acid oxidation, complete disposal of fatty acids and CPT-1 activity (the rate-limiting step in the mitochondrial fatty acid entry) were reduced in the livers of 5-week-old OLETF rats prior to the development of insulin resistance and NAFLD, indicating mitochondrial function impairment in liver steatosis. Therefore, mitochondrial fatty acid oxidation decrease and triglyceride accumulation occur[69]. Haque M. *et al* reported that mitochondrial DNA is severely depleted in patients with NAFLD. This decline leads to lower polypeptide expression and lower activity of complexes I, III, IV and V, which consequently leads to mitochondrial dysfunction[70,71]. Several mechanism have been hypothesized for defects on mitochondrial respiratory chain (MRC) during fatty liver disease, Higher level of cytochrome P450 2E1 and lower level of mitochondiral GSH as a consequent of ROS overproduction. TNF-a is also able to induce hypoxia-inducible factor-1a [HIF-1a], and finally damage mitochondrial DNA, Morover it over activate nitric oxide synthetize[3] that results in more ROS and progreesive decrease in MRC activity. As mentioned above Kupffer cell-derived interferons can impair the activity of MRC. Over activation of and FOXO1 is able to decrease MRC activity by reducing the peroxisome proliferators activated receptor G coactivator 1a (PGC1a) activity[72,73]. PGC1a is a transcriptional regulator that coordinates mitochondrial biogenesis. CR through AMPK phosphorylate and increase intracellular NAD+ level and increase PGC-1α activity, It also deactivate HIF-1a through SIRT1[60].

4. Sirtuins

Sirtuin1 is a NAD+-dependent deacetylase that is regulated by cellular energy. It links metabolic status to transcriptional outputs. Mammals have seven different sirtuins (SIRT1-7) that play important roles in gene silencing, DNA repair, rDNA recombination and aging in different organisms[74]. SIRT1 deacetylates many substrates, such as P53, FOXO, NF-Kb, Ku70 telomeric protein (a DNA repair factor), PGC-1 and so on, which generally relate to stress resistance activity of this enzyme. SIRT1 can also promote cell survival of pancreatic β-cells during oxidative stress and regulate stress glucose-stimulated insulin secretion in pancreatic β-cells[75,76]. Liver X receptors (LXR) are nuclear receptors that regulate cholesterol levels by inhibiting the absorption of cholesterol from the intestines, transmitting the cholesterol efflux HDL, and finally transporting the cholesterol to bile acid and stimulating excertion. Studies suggest that SIRT1 can activate LXR.

Furthermore, an interaction of SIRT1 with FOXO leads to the activation of detoxifying enzymes such as superoxide dismutase 2 (SOD2/MnSOD), catalase, and the reduction of intracellular oxidative stress[43,77]. The NF-Kb is a transcriptional factor, whose incorrect regulation leads to the activation of inflammatory processes, and is one of the main reasons for NAFLD. Studies suggest that SIRT1 deacetylates the RelA/p65 subunit, and inhibits NF-Kb signaling. Also, the acetylation of PGC-1a by SIRT1 leads to the activation of this nuclear factor, resulting in greater ATP production with lower

oxygen consumption, which consequently results in reduced ROS[78]. Dange *et al* reported that, following a 3-month high fat diet in male-Wistar rats with NAFLD, the expression of SIRT1 was reduced, while after calorie restriction, the level of SIRT1 was increased[78]. Also, Pluger *et al* showed that SIRT activators can protect mice from hepatic steatosis following a high-fat diet[79]. Recent data revealed that Sirt1 promotes ubiquitination and proteasomal degradation of SREBP1 and reduce lipogenesis in the liver[80]. Many studies reported that CR is the main activator of SIRT1, and many health benefits of this dietary intervention are mediated through this enzyme, so it can be concluded that patients with NAFLD may benefit from CR[77,81,82].

5. PPAR

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that play an important role in biological processes and metabolism. They have three isoforms, and despite their similar structure, are different in distribution and biological activity[83]. PPARα controls and regulates fatty acid β-oxidation in mitochondria and peroxisome and ω-oxidation in microsome. Ineffective PPAR-α sensing can lead to reduced energy-burning, resulting in hepatic steatosis and steatohepatitis[84]. PPAR-α deficiency in the mouse model has also been shown to aggravate inflammation and liver steatosis, indicating the protective role of PPAR-α[85]. Corton *et al* reported that 19% of CR-altered hepatic genes involved in lipid metabolism, inflammation, and cell growth were dependent on PPAR-α[86]. AMPK activation by calorie restriction increases fatty acid oxidation through PPARα and PGC-1α[87]. PPAR-γ is expressed in adipose tissue, the lower intestine, and cells involved in immunity, and is a mediator in glucose and lipid metabolism that increases glucose uptake in liver, adipocyte and skeletal muscle cells[88].

Adipocytes differentiation and triglyceride storage is a result of PPARγ activation[89]. PPARγ is the target receptor for thiazolidinedione, a drug in the insulin-sensitizing class. Paradoxically, recent data has shown that mice deficient in PPARγ are protected against insulin resistance, and that lower levels of PPAR could mitigate an age-related decline in insulin sensitivity[90]. Studies suggest that CR can hinder age-related decrease in PPARS[91]. In food scarcity, SIRT1 down-regulates the genes controlled by PPARγ and decreases fat storage[92]. Another study showed that 30% calorie restriction is not able to change RNA or protein levels of hepatic PPARγ in mice[93]. Treatment with PPAR-a or -γ agonist improved liver histology, compared with that of the NAFLD group. Significant fasting blood glucose reduction, alongside lower levels of triglyceride and cholesterol, have been reported after treatment[94].

DISCUSSION

The key step in finding the most effective treatment for NAFLD is to understand and recognize the altered mechanism. In this review, the main focus was on the mechanism involved in NAFLD initiation and progression, and the possible ways in which calorie restriction may affect and attenuate them.

In summary, CR can upregulate energy-sensing pathways, including AMPK/SIRTUIN, and down-regulate insulin signaling pathway IGF1/PI3K/AKT[19,38]. In NAFLD, the overactivation of AKT through PI3K-active mTOR and the recruitment of FOXO is followed by the regulation of gluconeogenic and lipogenic enzyme expression, IR, decreased autophagy, and liver cells apoptosis. Moreover, AMPK and SIRTUIN improve depleted mitochondrial DNA through activating and inactivating PGC1α and HIFα, respectively. SIRT1 can also reduce inflammation by deactivating NF-

kb and by up-regulating detoxifying enzymes through FOXO[56,60]. AMPK activation also increases fatty acid oxidation through PPARα, and SIRT1 down-regulates the genes controlled by PPARγ and decreases fat storage[76,77]. Moreover, it is well stablished that calorie restriction increase SIRT1-induced autophagy and decrease liver fat content which is regulated by autophagy[95]. It is postulated that possible interventions which may attenuate the over-activation of the insulin signaling downstream pathway may be the most effective. It seems that interventions which include CR in parallel with CR mimetic specifically those that upregulate SIRT1 as the superior agent of the mentioned pathway, can be effective strategies to alleviate NAFLD and reduce liver fat content[96,97]. Petersen *et al* previously shown that hypocaloric diet resulting 10% weight loss lead to insulin sensitivity improvement[98]. Three days low calorie diet reduced liver acetyl COA content, glycogenolysis and triglyceride-deacyl glycerol PKC activation that is followed by an overactivated IRS-associated-PI3K activity[99,100]. Remarkable evidence suggests that while IGF-1/PI-3K/AKT signaling enhances the growth of animals, they can potentiate the aging process later in life, which is called the insulin/IGF-1 paradox[101]. Several studies suggest that the deregulation of the PI3K/AKT pathway in hepatocytes is a common molecular event, one which is associated with metabolic disorders such as metabolic syndrome, obesity and NAFLD[102].

As discussed, the alteration in FOXO, mTOR, RAS/MAPK, and JNK in the insulin signaling pathway may lead to NAFLD. However, the exact role of FOXO on NAFLD is unclear. In some cases, FOXO acts against NAFLD via activating detoxifying enzymes[103], while in others, FOXO induces IR and promotes NAFLD[39]. It is therefore suggested that studies be designed to evaluate the exact effects of calorie restriction on FOXO and its consequences on NAFLD, but over different periods and intensity levels; it is postulated that activating FOXO may be profitable due to increased detoxifying enzyme activity, autophagy and hepatocyte survival, but it may also promote IR and induce inflammation through IL1β and NFKβ.

It seems that interventions which include CR in parallel with CR mimetic specifically those that upregulate SIRT1 as the superior agent of the mentioned pathway, can be effective strategies to alleviate NAFLD and reduce liver fat content[96,97]. In this regard epigenetic diet (dietary compounds which alter gene expression without changing DNA sequence) that include dietary compound that mimics calorie restrictions pathway without reducing calorie limitations can synergically work on NAFLD[104,105].

CONCLUSION

Epidemiological studies indicate that the prevalence of NAFLD, known as the accumulation of excess fat in the liver in the absence of significant alcohol consumption, is rapidly increasing. Until now, there has been no specific medical treatment for NAFLD, however, it is recommended to restrict calorie intake, in addition to increasing physical activity. Understanding the exact mechanism involved in NAFLD, and the ways in which different treatments can attenuate them, is a key point in finding the most effective treatment. Sirtuins, FOXO, and AMPK are the well-known molecules which mediate CR effects; moreover, increasing autophagy and mitochondria biogenesis through CR are important factors which play a role in disease prevention. These molecules and biological events are disturbed in NAFLD, and CR can invert or regulate them in many cases. Finding the most effective mediator and regulating it, which is probably involved in insulin signaling, can contribute to the development of new therapeutic strategies.

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Peer Reviewer: Monica de Miranda Henriques