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Fructose-induced inflammation and increased cortisol: A new mechanism for how sugar induces visceral adiposity

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ABSTRACT

Traditionally, the leading hypothesis regarding the development of obesity involves caloric imbalance, whereby the amount of calories consumed exceeds the amount of calories burned which causes obesity. Another hypothesis for why we get fat has surfaced in the last decade which is the idea that the overconsumption of added sugars and refined carbohydrates induce insulin resistance and high insulin levels causing obesity. While insulin is a fat-storing hormone, this hypothesis does not explain visceral adiposity, or why certain people are found to have fat stored in and around their organs. We propose a new mechanism for body fattening, particular visceral adiposity. This hypothesis involves the overconsumption of fructose, which leads to inflammation in all cells that metabolize it rapidly. When fructose is metabolized in subcutaneous adipocytes, the subsequent inflammation leads to an increase in intracellular cortisol in order to help squelch the inflammation. Unfortunately, the increase in intracellular cortisol leads to an increased flux of fatty acids out of the subcutaneous adipocytes allowing more substrate for fat storage into visceral fat tissue. Moreover fructose-induced inflammation in the liver also leads to increased intracellular cortisol via an upregulation of 11-B hydroxysteroid dehydrogenase type 1 causing increased fat storage in the liver (i.e., fatty liver). In essence, the fructose-induced inflammatory cortisol response causes "thin on the outside, fat on the inside" (TOFI). Furthermore, fructose in the brain, either from fructose uptake via the blood brain barrier or endogenous formation from glucose via the polyol pathway stimulates an increased release of cortisol causing hepatic gluconeogenesis leading to overall insulin resistance and further body fattening. This review paper will discuss in detail the hypothesis that fructose-induced inflammation and cortisol activation causes visceral adiposity.

Contents

Abbreviations: 11β-HSD1, 11B-hydroxysteroid dehydrogenase-1; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DHAP, dihydroxyacetone phosphate; FFA, free fatty acids; HFCS, high-fructose corn syrup; IRS1, insulin receptor substrate 1; ICAM-1, intracellular adhesion molecule-1; KHK, ketohexokinase; MetS, metabolic syndrome; MCP-1, monocyte chemoattractant protein-1; PVN, paraventricular nucleus; PFK, phosphofructokinase; SCAT, subcutaneous adipocyte tissue; T2D, type 2 diabetes; TOFI, thin on the outside, fat on the inside; TNF-α, tumor necrosis factor-alpha; VAT, visceral adipocyte tissue; WAT, white adipose tissue.

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Dietary intake plays a very important role in regulating one's health. Carbohydrates in the diet are broken down into simple sugars (glucose). However, if one consumes a diet containing sugar (glucose and fructose), these monosaccharides get absorbed and metabolized differently. Fructose in particular, is not only metabolized differently than glucose but is also not regulated by insulin. Its metabolism can also lead to significant inflammation and visceral adiposity whereas overconsuming glucose primarily leads to increases in subcutaneous fat.[1,2]

Insulin acts by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue. While insulin does promote subcutaneous fat storage, its selective role in promoting visceral adiposity is not as convincing as it seems. Major problems arise, when excess sugars are chronically consumed in the diet, especially when one already has underlying inflammation, insulin resistance and/or visceral adiposity. And insulin resistance itself is thought to lead to an array of comorbidities comprising of obesity, dyslipidemia, type-2 diabetes (T2D), hypertension, and coronary artery disease.[3]

One of the most important factors driving insulin resistance and chronic hyperglycemia is the overconsumption of added sugars (high-fructose corn syrup and sucrose, also known as table sugar). These added sugars consist of both glucose and fructose, of which the latter plays a larger pathological role.[4–7] In fact, compared to glucose or dextrose, sucrose or isolated fructose seems to be worse at promoting insulin resistance, T2D, and chronic kidney disease.[6]

Over the last two hundred years, the intake of added fructose in the diet has been on the rise and there is evidence from both observational and clinical trials indicating that excess fructose intake could lead to prediabetes and T2D.[6] Fructose, particularly from high-fructose corn syrup (HFCS), which is frequently used in various processed foods and soft drinks, is associated with insulin resistance.[8] Consumption of fructose at current intakes around the world triggers a cascade of events originating in the liver, which includes lipogenesis, hypertriglyceridemia, hepatic steatosis, and insulin resistance.[2,9–13] Fructose is responsible for the downregulation of insulin binding and insulin sensitivity which subsequently results in insulin resistance.[2,14]

Due to fructose-induced inflammation there is also an increase in 11B-hydroxysteroid dehydrogenase-1. This leads to an increase in intracellular cortisol in subcutaneous adipocyte tissue (essentially making them insulin resistant) causing less fatty acids to enter the subcutaneous adipocyte while more are expelled for storage into visceral depots and in and around organs, such as the liver, skeletal muscle, heart, and pancreas, further disrupting metabolic processes and impairing organ function.[15,16,17] Thus, overconsumption of added sugars (sucrose and HFCS) promotes "thin on the outside, fat on the inside" (TOFI).

The term TOFI is used to describe lean individuals with an increased fat deposition within their abdomen (visceral adiposity).[18,19] Subjects with TOFI have a body mass index < 25 kg/m^2 with an increase in risk factors associated with the metabolic syndrome. This phenotype is a subtype of "metabolically-obese but normal-weight".[20–22] The prevalence of TOFI is uncertain but a recent study by Thomas E. L. et al. estimated that 14% of men and 12% of women have TOFI.[19] TOFI can be diagnosed by MRI or CT scan which can help in differentiating fat (bright white) and other tissues (dark).

Visceral versus subcutaneous fat storage

Fat stored below the skin is known as subcutaneous fat and when it gets stored within the abdominal cavity, it is known as visceral adiposity. Visceral fat, also referred to as abdominal fat, is stored underneath the peritoneal cavity and is more active in secreting proinflammatory cytokines. Thus, storing visceral fat is more metabolically harmful as compared to subcutaneous fat (fat stored just beneath the skin). A protruding belly and large waistline is a clear indicator of visceral fat accumulation. While it is more noticeable in obese individuals, anyone can have visceral fat even those who are considered thin (hence the term TOFI).

When compared with subcutaneous adipocyte tissue (SCAT), visceral adipocyte tissue (VAT) is more vascular, cellular and innervated. It contains a greater number of immune cells and large adipocytes when compared to that of SCAT. There are also more androgen and glucocorticoid receptors in VAT than in SCAT. Adipocytes in VAT are not only more metabolically active but also are more sensitive to lipolysis than adipocytes in SCAT. VAT also generates higher amounts of free fatty acids, has an enhanced uptake of glucose and a higher sensitivity to adrenergic stimulation, while SCAT is more involved in absorbing circulating free fatty acids and triglycerides (TGs).[23] Overall, VAT accumulation increases the risk of metabolic disorders, such as T2D, hypertension, hyperlipidemia and atherosclerosis, as well as premature mortality.[24–31]

Current dietary practices with regards to fructose

Sucrose (or table sugar) and high-fructose corn syrup (HFCS) are made up of both fructose and glucose with a ratio of 50:50 (for sucrose) and 55:42 (for HFCS), respectively. The overconsumption of these added sugars has been implicated in causing fatty liver and insulin resistance.[32,33] While it was previously thought that fructose may be more beneficial on glycemic control as it has a lower glycemic index,[34,35] it is now recognized that fructose has chronic deleterious effects on health with respect to obesity, T2D and atherosclerosis.[32]

While added fructose is found in various industrial food products it is also a component of fruits, berries and vegetables, which are not associated with metabolic harms. The intake of added fructose in liquid form began to increase around the 1950s, particularly due to an increased consumption of sugar-sweetened beverages.[36] In 2004, the average intake of fructose in America was estimated to be around 50 g per person per day.[37]

Absorption and metabolism of fructose

The process of fructose absorption is not entirely understood, but it is suggested that its absorption takes place at the jejunum via the GLUT-5 transporter. GLUT5 is also expressed in the membranes of adipocytes, kidney, muscle, and brain cells.[38] After absorption, fructose is carried on to the liver where it is primarily metabolized.[39]

While glucose and fructose have similar structures, their metabolism is quite different.[40] In contrast to glucose, the metabolism of fructose is not regulated by insulin. Fructose bypasses the regulated steps in metabolism including the main phosphofructokinase (PFK) step, finally entering as fructose-1-phosphate after phosphorylation by fructokinase/ketohexokinase (KHK).[41] PFK is tightly regulated by the energy status of the cell. Unlike the phosphofructokinase in glycolysis, fructokinase is not inhibited by ATP.[42]

Hence, even when ATP in the liver is high, fructokinase will metabolize fructose to form fructose 1-phosphate which is then cleaved to dihydroxyacetone phosphate (DHAP) and glyceraldehyde by the enzyme aldolase B. Glyceraldehyde can be further phosphorylated to glceraldehyde-3-phosphate which can either continue in the glycolysis pathway and synthesis of fatty acids via acetyl-CoA or it can even form glycerol-3-phosphate, subsequently helping in triglyceride synthesis.[33] In addition, fructose is known to upregulate the C isoform of KHK

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(KHK-C) which is highly active and present in liver.[43] Excess fructose can be metabolized at a very high rate in liver by KHK-C and can lead to the formation of Acetyl Co-A (a substrate for fatty acid synthesis) which subsequently increases lipogenesis. The overproduction of FFAs then either gets released or stored in the liver.

Fructose causing inflammation and insulin resistance in adipocytes and liver

The overconsumption of added fructose provokes metabolic changes that result in a chronic low-grade inflammation, insulin resistance and adiposity.[44] Fructose over-consumption has tissue-specific effects on the regulation of metabolic inflammation. Several studies have shown that the overconsumption of fructose can lead to an increase in macrophage infiltration (via monocyte chemoattractant protein-1 [MCP-1] and intracellular adhesion molecule-1 [ICAM-1] induction) into adipocytes.[45–47] Increased macrophage recruitment into the adipocytes is the cause of the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) leading to further inflammation.[47]

A study done by Shapiro et al., showed fructose consumption causes leptin resistance leading to an increase in leptin levels with no effect on fat mass.[48] High leptin levels are also known for causing inflammation in adipocytes. Leptin can lead to the release of reactive oxygen species and can also cause the recruitment of monocytes perpetuating further inflammation.[49]

Inflammation leads to an increase in 11β-HSD1 activity which increases cortisol levels within the cell. This further leads to insulin resistance and increase in the flux of fatty acids out of the subcutaneous adipocytes allowing more substrate for fat storage into visceral adipocytes. Fructose intake may also induce hypertriglyceridemia and lipogenesis mainly in the liver and muscles rather than in the adipose tissue.[50,51] Since fructose consumption does not lead to insulin stimulation, it may contribute to a decrease in clearance of triglycerides (TGs).

Visceral adipocytes are fed via the portal circulation; FFAs released from subcutaneous adipocytes can get deposited into visceral adipocytes. FFAs can also directly enter the liver via the portal circulation from visceral adipocytes and cause metabolic disturbances in the liver.[52–54]

As FFA are released by adipose tissue and deposited in the liver, the liver tries to oxidize or esterify them to form TGs, which are first stored and later secreted in very low density lipoproteins (VLDL).[55–56] However, when the rate of FFA oxidization or esterification increases more than the rate of VLDL formation and secretion, FFA starts depositing in the liver.[55] It has been suggested that TG deposition in the liver is a major cause of hepatic insulin resistance.[57,58] Morino et al. derived a mechanism which showed that intracellular lipid causes insulin resistance in both liver and muscle.[58]

Hepatic insulin resistance leads to increased VLDL production and reduced apoB degradation.[59] Elevated TGs and plasma FFA (released from insulin-resistant adipose tissue) can also be deposited into other tissues. Such deposition produces metabolites such as diacylglycerol (DAG), which is responsible for triggering the activation of Protein kinase-C (PKC) leading to insulin resistance.[60–62] PKC is responsible for the production of reactive oxygen species (ROS) via NADPH oxidase activation. ROS also activates IκB kinase (IKK), which is another serine/threonine kinase. IKK can also be activated by PKC directly. PKC and IKK activation are responsible for the serine phosphorylation of IRS-1, thus, inhibiting its tyrosine phosphorylation, which is necessary for proper insulin signalling.[63–65] All of this leads to, improper insulin signalling and finally insulin resistance. IKK also leads to activation of pro-inflammatory transcriptional factor and NF-Kappa B. Activation of the NF-kappa B pathway subsequently induces production of a number of other pro-inflammatory cytokines like TNF-α, IL1-β, IL-6 and macrophage chemoattractant protein-1(MCP-1),[61,62] which are responsible for macrophage recruitment to the site of inflammation.[63] This also explains the mechanism of FFAs triggering inflammation in the liver.

Glucocorticoids: background and roles in fructose-induced inflammation

Glucocorticoids (cortisol and cortisone are present in man while corticosterone and dehydrocorticosterone are present in rodents) are synthesized in and secreted from the zona fasciculata of the adrenal gland, under the regulation of adrenocorticotropic hormone (ACTH) which is secreted from the anterior pituitary gland. The secretion of ACTH is under the control of corticotropin-releasing hormone (CRH) and vasopressin which are secreted from the hypothalamus. This complex set of hormone interactions and regulations is often referred to as the hypothalamus–pituitary–adrenal (HPA) axis.[66]

Glucocorticoids are potent immunosuppressors which are routinely used in the treatment of various chronic inflammatory diseases. In physiological concentrations, they exhibit various anti-inflammatory effects and are known to suppress the inflammatory process. In response to inflammation, the HPA axis is activated by an increase in circulating pro-inflammatory cytokines such as adipokine leptin, TNF-α and the interleukins (IL-1 and IL-6).[65,67]

The association of glucocorticoids with human visceral obesity and its related metabolic disorders, is a matter of significant interest. This is not only evident in subjects with HPA axis imbalance [i.e. patients with Cushing's syndrome and Addison's disease] but also in conditions where tissue glucocorticoids are locally modified.[68,69] Overall, the HPA-axis as well as 11β-HSD-1 is activated by an increasing amount of cytokines due to excess consumption of fructose, causing secretion of glucocorticoids to combat inflammation.[64,65] TNF-alpha and monocyte differentiation into macrophages induces 11β-HSD1 gene expression in various cell types such as adipocytes, fibroblasts and myocytes, whereas hepatic inflammation is mediated by NF-kappa B and IKK.[64,70–72]

Fructose increases intracellular cortisol via 11β-HSD1

It is well-known fact that excess cortisol can also induce fat accumulation in the central part of the abdomen, facial, dorsocervical region (buffalo hump) and arterial walls.[73–77] 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) isoenzyme activates cortisol from cortisone in men and corticosterone from 11-dehydrocorticosterone in rodents. Cortisone and 11-dehydrocorticosterone are inactive corticosteroids which are activated by 11β-HSD-1 to their active forms.[78–80]

11β-HSD-1 is widely expressed in the liver and it utilizes the co-factors such as NADP+ or NADPH to catalyse both dehydrogenation and the reverse oxo-reduction reaction (cortisone and 11-dehydrocorticosterone to cortisol and corticosterone, respectively) in which, the latter activity is more prominent in vivo due to co-existence of hexose-6-phosphate dehydrogenase (H6PD).[81] H6PD preserves the oxo-reductase activity by generating NADPH, suggesting the importance of co-factor availability which can dictate the direction of activity of 11β-HSD-1.[82] Thus, it regulates the glucocorticosteroid response.[66] In contrast, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) is an NAD+-dependent dehydrogenase enzyme which inactivates cortisol and corticosterone in man and mice, respectively.[83]

As a result, the 11β-HSD-1-dependent reaction produces active glucocorticoids which bind to the glucocorticoid receptor in glucocorticoid target tissues like adipose tissue, lung and liver, while the 11β-HSD-2 dependent reaction hinders the binding of glucocorticoids to the non-selective mineralocorticoid receptor in organs like kidney and colon. Hence, glucocorticoid response not only relies upon systemic glucocorticoid levels and intracellular GR activity, but also on intracellular amplification or elimination of bioactive glucocorticoids by 11β-HSD-1.[66]

During the last decade, evidence has strongly suggested that the levels of 11β-HSD-1 play an etiological role in obesity and the metabolic syndrome.[84–90] At the same time, there are also studies which support the role of 11β-HSD-1 in inflammation.[70,91–96] Increased 11B-HSD-1 activity in VAT due to fructose-induced inflammation leads to an increased cortisol level within adipose tissue and liver and subsequently,

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it promotes the features of the metabolic syndrome.[86,97] In one study, transgenic mice who were overexpressing 11β-HSD-1 in the adipose tissue were found to have the metabolic syndrome[84,87,97] and 11β-HSD-1 KO (Knock out) mice or rodents treated with 11β-HSD-1 inhibitors were found to be protected from cardio-metabolic risk of obesity.[87] Hence, 11β-HSD-1 functions as an important regulator of inflammation and visceral adiposity. In a recent review done by Staab et al., it was observed that 11β-HSD-1 plays an important causative role in the development of the metabolic syndrome.[66] 11β-HSD-1 is thus, nowadays recognized as a promising drug target in the current obesity epidemic. Through amplification of the glucocorticoid receptor, 11β-HSD-1 enhances glucocorticoid responses with significant consequences regarding the expression of genes involved in metabolic disease and inflammation.

11β-HSD1 regulation and its actions

The two main factors regulating the levels of 11B–HSD are the levels of H6PD in the lumen of endoplasmic reticulum and generation of pro inflammatory mediators like TNF-α and IL-1. Several functional studies suggested that H6PD activity within the lumen of the endoplasmic reticulum plays a critical role in regulating the oxo-reductase activity of 11β-HSD-1 by providing NADPH.[70] The consumption of a fructose-rich diet enhances the production of H6PD in turn facilitating activity of 11β–HSD-1 in generating active cortisol within the visceral adipose. It was also shown more than a decade ago that obesity is associated with an induction of TNF expression in white adipose tissue (WAT) as well as an increase of systemic TNF-alpha protein, depletion of which can lead to an increase in insulin sensitivity.[47]

11β-HSD-1 gene expression is induced in monocytes during its differentiation into macrophages.[64] Moreover, in adipocytes, 11β-HSD-1 gene expression is not only induced by TNF-alpha and IL-1[70,72,98] but also, correlates positively with adipocyte size.[97,99] However one study has found that 11β-HSD-1 expression is not increased in liver indicating tissue-specific differential regulation.[100] Thus, inflammation leading to a rise in 11β-HSD-1 activity in adipose tissue probably raises local tissue and hepatic portal vein cortisol concentrations giving rise to a Cushing syndrome-like effect, i.e. inducing hyperglycemia and insulin resistance followed by exacerbation of obesity, without affecting the concentration of systemic glucocorticoid overall. It was shown that following oral cortisone administration, the levels of cortisol regenerated in the liver was one-third while the other two-thirds were likely from visceral components (mostly in the visceral adipose tissue).[101] This suggests that effect of 11β-HSD-1 is greater in the visceral adipose tissue which leads to accumulation of fat selectively in the visceral organs by enhancing the glucocorticoid response at the pre-receptor level. Accordingly, overexpression of 11β-HSD-1 transgenetically leads to an increase in intra-adipose concentration of glucocorticoids within adipose tissue.[84,97]

It has also been noted that 11β-HSD-1 has a profound effect on altering insulin sensitivity. 11β-HSD-1, when inhibited pharmacologically with the anti-ulcer drug carbenoxolone, proved the influence of cortisol regeneration on alteration of insulin sensitivity, particularly glycogen turnover, in healthy human subjects and in patients with T2D.[102,103] This suggests that 11β-HSD-1 induced glucocorticoid response alters the insulin sensitivity for which one of the possible mechanisms could be a glucocorticoid response disrupting the insulin signalling cascade and resulting in insulin resistance by inactivation of IRS-1 protein by serine phosphorylation and downregulation of IRS-1 gene expression.[104]

Thus, an overconsumption of added fructose may increase 11β-HSD-1, which increases intracellular cortisol and preferentially stimulates visceral fat storage. The increase in 11B-HSD1 likely occurs to help squelch inflammation but at the same times promotes storage of fat in organs.[64,70,91–96] The expression of 11β-HSD-1 is directly proportional to adipocyte size.[97,99] The increase in 11β-HSD-1 is responsible for the local increase in cortisol concentration in the tissues and the portal vein, which in turn is responsible for the hyperglycemia, insulin resistance and visceral obesity exacerbation.[85–89,105–107]

Fructose in the brain stimulates the HPA-axis and cortisol secretion

GLUT5 transporters are present in the blood-brain barrier, which suggests that circulating fructose can enter the brain.[38] Moreover the polyol pathway (which converts endogenous glucose to fructose) resides in the brain and hence fructose likely has physiological effects in the brain via endogenous fructogenesis from glucose.[108] Fructose has also been found to stimulate the hypothalamus, which induces hepatic gluconeogenesis via corticosterone release from the adrenal gland.[109] Fructose administered either intraperitoneally or intracerebroventricularly triggers phosphorylation of energy sensing AMPK in neurons of paraventricular nucleus (PVN) of hypothalamus. The PVN releases CRH, which stimulates the release of ACTH from the anterior pituitary, which in turn stimulates the production of corticosteroids from the adrenal glands. The corticosterone induces the expression of PEPCK eventually increasing hepatic gluconeogenesis and glucose excess in blood, i.e. hyperglycemia. This has been termed “sugar making sugar”. Corticosteroid induces insulin resistance via downregulation of insulin receptor substrate 1 (IRS1) gene expression and inactivating serine phosphorylation of IRS1 proteins through 11B-HSD1, thus, distorting the insulin cascade.[104] Fig 1 summarizes how fructose induces inflammation, intracellular cortisol, and visceral adiposity.

Downregulated PEPCK induced increase in release of FFA from adipocytes

PEPCK enzyme is primarily involved in gluconeogenesis and regulation of lipid metabolism.[110] Fructose-induced inflammation and increase in glucocorticoids can have an impact on PEPCK transcription. Increases in glucocorticoids leads to an increase PEPCK transcription in liver while PEPCK transcription decreases in adipocytes. Since PEPCK upregulation leads to adipocyte lipid storage and decrease in FFA release from the adipocytes, its downregulation can lead to a decrease in lipid storage in adipocytes and an increase in FFA release overall.[111,112] It may further lead to deposition of FFA in the liver.

Fructose and weight gain

A systematic review of systematic reviews indicated that 83.3% of studies without conflicts to the food industry find a positive association between sugar sweetened beverages and weight gain or obesity.[113] A systematic review and meta-analyses of randomised controlled trials and cohort studies concluded that among free living people ad libitum intake of free sugars or sugar sweetened beverages is a determinant of body weight, which may be mediated by increased hunger and energy intake when more sugar is added into the diet.[114] Fructose can lead to insulin resistance and leptin resistance, which may increase hunger and delay satiety.[115] All of these harmful effects may drive obesity, MetS, TOFI, and cardiovascular disease.[116,117]

Conclusion

No matter how sweet it is to taste, added fructose (from sucrose and high fructose corn syrup) should be avoided in the diet, whereas consuming fruit seems to provide health benefits. Due to fructose induced inflammation and the subsequent increase in intracellular cortisol, visceral adiposity ensues. Indeed, fatty acids are subsequently released from the adipocytes to the visceral organs including liver, pancreas, skeletal muscle, and heart which can disrupt metabolic processes and impair organ function. However, a person may still look thin from outside, but overconsuming added fructose can lead to fat deposited in and around vital organs, which is known as “thin on the outside, fat on the inside” (TOFI). Hence, we propose that fructose makes one fatter from the inside due to an increase in visceral fat deposition partially caused by an increase in intracellular cortisol. Dietary guidelines should place limits on the consumption of added fructose to help reduce the risk of TOFI,

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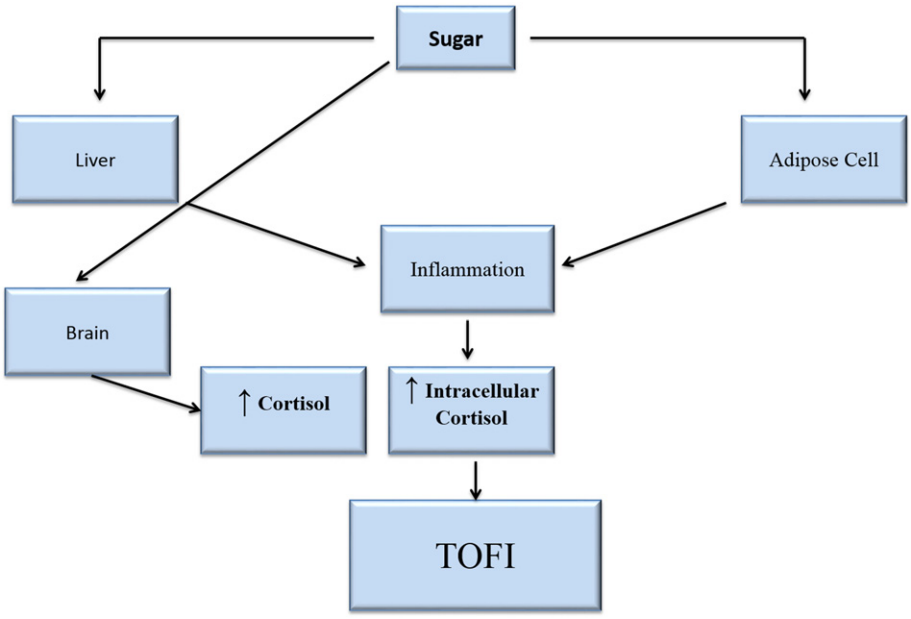

Fig 1. TOFI – thin on the outside, fat on the inside.

organ dysfunction, and cardiovascular disease. This should also help to decrease morbidity and mortality caused by these conditions.

Statement of conflict of interest

Dr. DiNicolantonio is the author of The Salt Fix and operates the website thesaltfix.com.

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