Aspartame: should individuals with Type II Diabetes be taking it?

Running title: Aspartame: with Type II Diabetes

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ABSTRACT

Background: Individuals with type II diabetes (T2D) have to manage blood glucose levels to sustain health and longevity. Artificial sweeteners (including aspartame) are suggested sugar alternatives for these individuals. The safety of aspartame in particular, has long been the centre of debate. Although it is such a controversial product, many clinicians recommend its use to T2D patients, during a controlled diet and as part of an intervention strategy. Aspartame is 200 times sweeter than sugar and has a negligible effect on blood glucose levels, and it is suggested for use so that T2D can control carbohydrate intake and blood glucose levels. However, research suggests that aspartame intake may lead to an increased risk of weight gain rather than weight loss, and cause impaired blood glucose tolerance in T2D. **Objective:** This review consolidates knowledge gained from studies that link aspartame consumption to the various mechanisms associated with T2D. **Method:** We review literature that provides evidence that raise concerns that aspartame may exacerbate T2D and add to the global burden of disease. **Result:** Aspartame may act as a chemical stressor by increasing cortisol levels, and may induce systemic oxidative stress by producing excess free radicals, and it may also alter gut microbial activity and interfere with the N-methyl D-aspartate (NMDA) receptor, resulting in insulin deficiency or resistance. **Conclusion:** Aspartame and its metabolites are safe for T2D is still debatable due to a lack of consistent data. More research is required that provides evidence and raise concerns that aspartame may exacerbate prevalence of pathological physiology in the already stressed physiology of T2D.

Key words: Aspartame, type II diabetes, glucose, insulin, weight gain

INTRODUCTION

Artificial sweeteners are low-calorie substitutes for sugar used to sweeten a wide variety of foods, has health controversy over perceived benefits[1]. The use of artificial sweeteners has increased concomitantly with a rising incidence of diabetes and allows type-II diabetics Individuals (T2D) to control carbohydrate intake and maintain blood glucose level, however artificial sweeteners have been linked to an increased risk of extreme weight gain, metabolic syndrome and cardiovascular complication [2-5].

"Lite or diet" carbonated soft drinks contain 150-200 mg of aspartame per serving (12 oz or 360 ml) and noncarbonated beverages usually contain 140 mg per serving (8 oz or 240 ml)[6, 7]. The European Food Safety Authority established acceptable daily intake (ADI) of aspartame by humans at 40 mg/kg.bw/day[8].The U.S. Food and Drug Administration (FDA) established an ADI of 50 mg/kg.bw/day[9]. Some authorities suggest that it is particularly useful for persons with T2D to use aspartame (up to ADI levels), as it has no significant effect on plasma glucose levels or blood lipids[10]. Aspartame may not influence on food intake, satiety levels or postprandial glucose levels, it may not have an effect on postprandial insulin levels compared to natural sweeteners such as sucrose[11]. Whilst aspartame consumption may assist with weight management by reducing caloric intake compared to sucrose[12], but there is evidence that rats may compensate for the reduction in calories by over eating, resulting in increased body weight and adiposity[13]. It is well-known that there is a concerning relationship between T2D and obesity[14] and that the increases in T2D prevalence are on the rise, even with governments and private sectors spending and increasing percentage of their funds on treating and caring for these individuals. Although the side-effects of aspartame are well-known such as neuroendocrine imbalances[15, 16], neurophysiological symptom[17], gut dysbiosis along with impaired blood glucose level[18, 19], altered liver function[20-22] and metabolic consequences[23]. However, people insist on its usefulness in particularly T2D. Therefore, in this paper we literature regarding the effect of aspartame [24, 25] and critically evaluate the mechanism of aspartame consumption in obese T2D (Figure 1) and raise important concerns regarding the safety of aspartame usage.

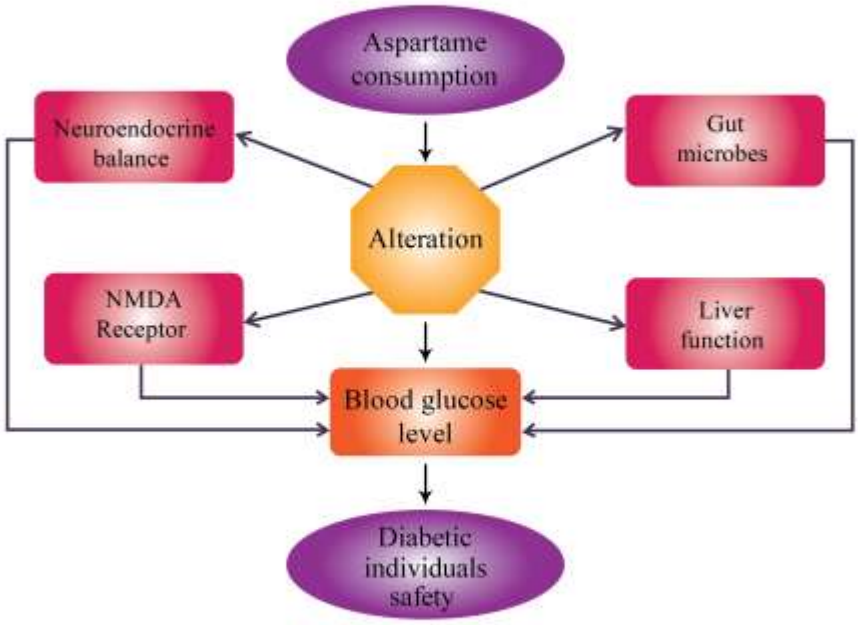

Figure 1: Aspartame consumption may lead to alteration of (a) neuroendocrine balances (b) N-methyl D-aspartate (NMDA) receptor (c) liver function, (d) gut microbes; this may result in impairment of blood glucose level in diabetic patients.

Aspartame and blood glucose levels

Aspartame is rapidly metabolized upon ingestion by gut enzymes (esterase and peptidase) into its metabolic components: phenylalanine (50%), aspartate (40%) and methanol (10%)[26]. Aspartame and its metabolites may cause the deregulation of blood glucose levels (see (Figure 1) by:

(1) Interruption of neuroendocrine balances [15, 16],

(2) Alteration of N-methyl D-aspartate (NMDA) receptor[27].

Table 1: Aspartame and studies looking at the maintenance of normal blood glucose levels.

Species	Study design	Observation	References
Mice	Aspartame (4g/kg.bw) dissolved in water and given to C57Bl/6 mice	At week 11, induced dysbiosis and glucose intolerance	[19]
Rat	Aspartame (5–7 mg/kg/d in drinking water) for 8 week.	Aspartame elevated fasting glucose levels	[18]
Human	Aspartame (290 kcal), preload 20 min before the lunch and dinner meal in healthy and obese individuals.	Postprandial glucose and insulin levels at 20 min after consumption were significantly lower compared to the sucrose condition	[11]
Mice	Aspartame alone (50 mg/Kgbw/day) and as well as with combination of Monosodium Glutamate (120 mg/Kgbw/day) were given to C57BL/6 J mice.	Significant increase in fasting blood glucose together with reduced insulin sensitivity during an Insulin Tolerance Test (ITT)	[30]
zebra fish	Aspartame (3 mM) were fed in the diet of hyperlipidemia, zebra fish nutritional model	Remarkable increase in serum glucose level after 12 days	[32]
Human	Aspartame-sweetened beverage (8 oz) was randomly assigned to drink in Sixty-four fasted participants.	No significant differences were observed in blood glucose level at 5, 10, and 15 min post-consumption.	[29]
Human	Ten healthy volunteers consumed one of three isovolumetric drinks (aspartame, 1 MJ simple carbohydrate, and 1 MJ high-fat; randomized order)	Aspartame ingestion was followed by blood glucose declines (40 % of subjects), increases (20 %), or stability (40 %). This varied blood glucose responses after aspartame support the controversy over its effects	[28]

(3) Impairment of liver function [20]

(4) Alteration of gut microbes [18].

The role of aspartame to maintain normal blood glucose level is controversial, in human [11, 28, 29] and animal studies[30-32] (Table 1). As, no significant differences were observed in blood glucose level [11, 29] , but however it's also fail to maintain normal level and raised blood glucose level[19, 30, 32] . Aspartame has also been linked to weight gain and hyperglycemia in common zebra fish nutritional model [32]. The chronic exposure of aspartame (50 mg/kg.bw), for first five months (mature adulthood) of life, deteriorates insulin sensitivity[30], and produces changes in blood glucose parameters and adversely impacts spatial learning and memory in mice [31]. It has also been found that aspartame exposure may cause behavioural differences and learning impairment in rodents[33-36]. Literature states that, learning impairments suggested to be linked to glucose homeostasis and insulin sensitivity, which affects neuronal survival and synaptic plasticity [37].

Aspartame and the neuro-endocrine balance

The disruptive effect of aspartame has been observed in the brains of aspartame treated mice[38]. The neuro-endocrine system maintains glucose homeostasis[39]. Glucose receptors (GLUTS) are mainly present in the liver, pancreas and brain[40]. The hypothalamic–pituitary–adrenal (HPA) axis maintains glucose homeostasis by augmenting liver glycogenolysis and gluconeogenesis [39]. Aspartame is a chemical stressor to the HPA axis and produces excess corticosterone (cortisol) [16]. Disrupted glucose homeostasis may cause hyperglycemia leading to insulin resistance[41]. A mild condition of unchecked hyperglycemia may be indicative of pre-diabetes; defined as having an impaired fasting glucose (IFG) (glucose level ≥ 100 mg/dL but ≤ 125 mg/dL) or impaired glucose tolerance [42] .

Aspartame may further affect glucose homeostasis by increasing muscarinic receptor density by 80% in the brain, including the hypothalamus [35]. The activation of muscarinic and ACh-receptive neurons (mAChRs) in the hypothalamus triggered an elevation in rodent plasma glucose levels, and reduced by the mAChRs antagonist, atropine, suggesting a role for hypothalamic mAChRs in glucose homeostasis[43].

Aspartame and the N-methyl D-aspartate (NMDA) receptor

N-methyl D-aspartate (NMDA) receptors are distributed throughout the central nervous system including the hypothalamus, amygdala and hippocampus, regulating vital metabolic and autonomic functions including energy homeostasis[44], glucose sensing [45] and non-

insulin mediated hepatic glucose uptake[46]. Aspartate, a component of aspartame, may activate the NMDA receptor and occupy binding sites for glutamate[26]. During hypoglycemia, central excitatory amino acids through activation of NMDA receptors, resulting in stimulation of the sympathoadrenal as well as hypothalamic–pituitary adrenal axis and appears to play an important role in the sustained elevation in hepatic glucose production[47]. Hence drinking aspartame sweetened drinks whilst in a hypoglycemic state may interfere with the glucoregulatory response.

Aspartame and the liver function

The liver maintains normal glucose concentrations during fasting and after eating, and it is a major site of insulin clearance[48]. Hepatic glucose production and glycogenolysis may result in hyperglycemia when insulin is absent or when the liver is insulin resistant[49]. Aspartame consumption at the safety dosage (40mg/kg.bw/day) may cause abnormal hepatocellular function[20-22, 32, 50]. The alteration of hepatic function is associated with a decline in hepatic insulin sensitivity and impairment of blood glucose level[51].

Aspartame and changes in appetite and weight

It was previously noted that aspartame may actually stimulate appetite, increase carbohydrate cravings, stimulate fat storage and increase weight gain [5].

Whilst aspartame is recommended to assist with weight management by reducing food intake and controlling calories [12]. The observed weight gains in aspartame fed rats, that consumed the same amount of calories as water fed rats, could be due to a decrease in energy expenditure or increases in fluid retention [13]. Higher BMI was observed in human with consumption of diet carbonated beverages containing aspartame[52, 53]

The body may use sweet taste to predict the caloric contents of food[54]. The sweet taste, regardless of caloric content, enhances our appetite[55]. The calories contained in natural sweeteners trigger biological responses to keep overall energy consumption constant. Non-caloric sweeteners may promote excessive intake and body weight gain by corrupting the predictive relationship between sweet taste and the caloric consequences of eating[5]. The unbalanced predictive relationship may lead to a positive energy balance through increased food intake and/or diminished energy[56]. Defective appetite control mechanisms may trigger food cravings[56] . weight gain has been linked to the increasingly widespread use of non-caloric artificial sweeteners, such as aspartame (e.g., Diet Coke) in food products [5]. The effects of aspartame on weight gain are summarized in (Table 2).

Table 2: Research showing the effects of aspartame on weight gain.

Species	Observation	References
Human	Higher BMI was observed with consumption of diet carbonated beverages.	[53]
Human	Increased diet soda consumption was associated with higher BMI in school children.	[52]
Zebra fish	Aspartame may promote weight gain and hyperglycemia in a zebra fish nutritional model	[32]
Mice	A positive association between aspartame intake and body weight in C57BL/6 J mice.	[29]
Rat	Aspartame can cause greater weight gain than sugar, even when the total caloric intake remains similar.	[13]

Energy balance is regulated through the manufacture of leptin (satiety hormone) by adipose cells and by inhibiting ghrelin, (the hunger hormone). Both hormones act on the receptors in the arcuate nucleus of the hypothalamus to regulate appetite[57]. Interestingly, research showed that the arcuate nucleus of the hypothalamus in adult mouse brains is damaged markedly by aspartame (0.5 mg/g) [36]. It is suggested that aspartame usage may upset appetite regulation and lead to weight gain, as aspartame do not activate the food reward pathways in the same fashion as natural sweeteners but encourage sugar craving and sugar dependence; lead to gain weight[5]. Usually changes in weight are related to changes in insulin receptor or insulin resistance[58]. Weight gain is related to increased insulin and glucose levels[59]. Chronically elevated insulin levels are associated with a decrease in insulin sensitivity [60] and may lead to eventual insulin resistance [58]. It is proposed that Insulin resistance is associated with impaired blood sugar, triglycerides, blood clots, sleep, as well as cardiovascular and neurological disorder [61-63] (Figure 2).

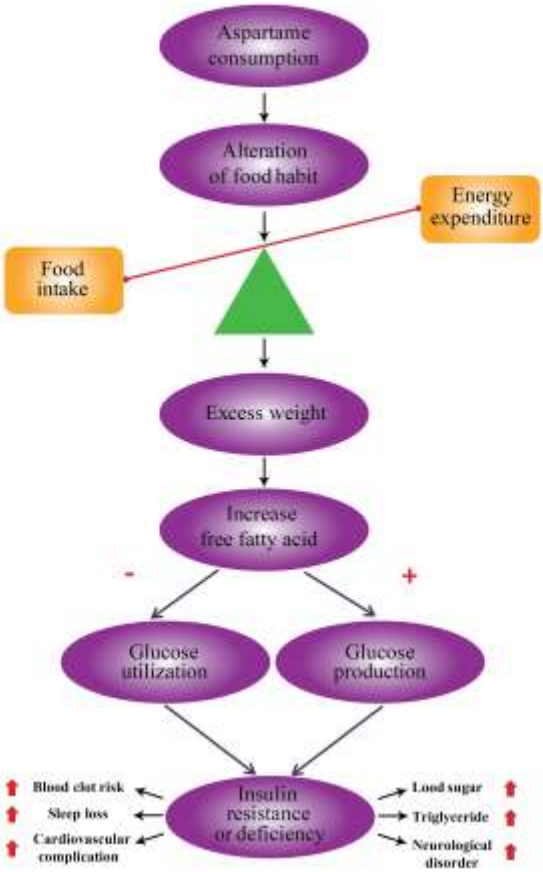

Figure 2: Aspartame consumption may alter food habits (satiety signal), lead to weight gain, increase free fatty acid, which may inhibit glucose utilization and promote glucose production and result in for insulin resistance or deficiency. Insulin resistance is associated with impaired blood sugar, triglycerides, blood clots, sleep, as well as cardiovascular and neurological disorder.

Aspartame and Gut dysbiosis with insulin resistance or deficiency

Gut microbes modulate main host biological systems that control energy homoeostasis and glucose metabolism in T2D [64] and plays a significant role in the development of insulin resistance[65]. The intestinal bacterial population unique to T2D may produce toxins causing systemic inflammation, affecting overall metabolism and insulin sensitivity[66]. Low dose aspartame (5–7 mg/kg/day) consumption in drinking water over eight weeks resulted in elevated fasting glucose levels and impaired insulin tolerance in diet-induced obese rats and the fecal analysis of gut microbiota showed aspartame to increase the abundance of *Enterobacteriaceae* [18]. Mice that drank water with 4% aspartame and consumed a high fat

diet for eleven weeks had higher glucose excursions after a glucose load, these changes were associated with a metabolic phenotype change caused by alteration of the gut microbiota [19] and dysregulated microbiota-gut-brain axis may explain aspartame metabolic and other side-effects [67].

Generally it is well-known that glucose intolerance is a precursor to T2D[68]. T2D is a heterogeneous disease with large variation in the relative contributions of insulin resistance and beta cell dysfunction [69]. Insulin is synthesized and released from pancreatic β- cells in response to increases in plasma glucose concentrations[70]. Increases in amino acids can influence insulin biosynthesis and secretion[71]. The amino acid; phenylalanine, may stimulate insulin secretion and glucagon concentration[72]. The insulin response can be substantially increased by phenylalanine, and has high insulinotropic potential in T2D[73].The amino acid; phenylalanine (50%), is a major aspartame component, may lead to insulin resistance or deficiency.

Cortisol pathway to insulin resistance

The cortisol pathway plays an important role in the development of insulin resistance, and literature suggests that aspartame (75mg/kg.bw/day), may act as a chemical stressor and result in the production of excess corticosterone (cortisol) after 90-days of oral administration in rats [16]. In general cortisol has been linked to insulin resistance through the following mechanism:

1. Cortisol decreases the translocation of GLUT-4 transports and associated glucose uptake[74, 75].
2. Cortisol inhibits the release of insulin from the beta cells of pancreas in mice[76].
3. Cortisol facilitates insulin resistance by increasing the production of glucose and accumulation of lipids in the cell [74, 75].

Rats given the safety dosage of aspartame (40mg/kg.bw/day) for 90-days, showed a significant increase in coticosterone level but no significant changes in blood glucose level [50]. But however, prolonged exposure to excess levels of cortisol may affect blood glucose levels in T2D[77]. Excess levels of cortisol may induce insulin resistance or decrease insulin action[78] (Figure 3A and B) which decreases both hepatic and extra hepatic (peripheral) sensitivity to insulin and increase blood glucose levels [74] (Figure 4A). Cortisol also increases the rate of gluconeogenesis and glycogenolysis in liver, and decreases the activity of the GLUT-4 transporter and related glucose uptake in skeletal muscle. Furthermore, it increases lipolysis and decreases the activity of lipoprotein lipase; both of which increase free fatty acid levels in the cell and compete with glucose for oxidative metabolism (Figure 4A) [74, 75]. Cortisol action therefore directly opposes insulin action and can be described

as a diabetogenic hormone, that fundamentally and possibly directly contributes to insulin resistance (Figure 3A and B) [74, 75].

A

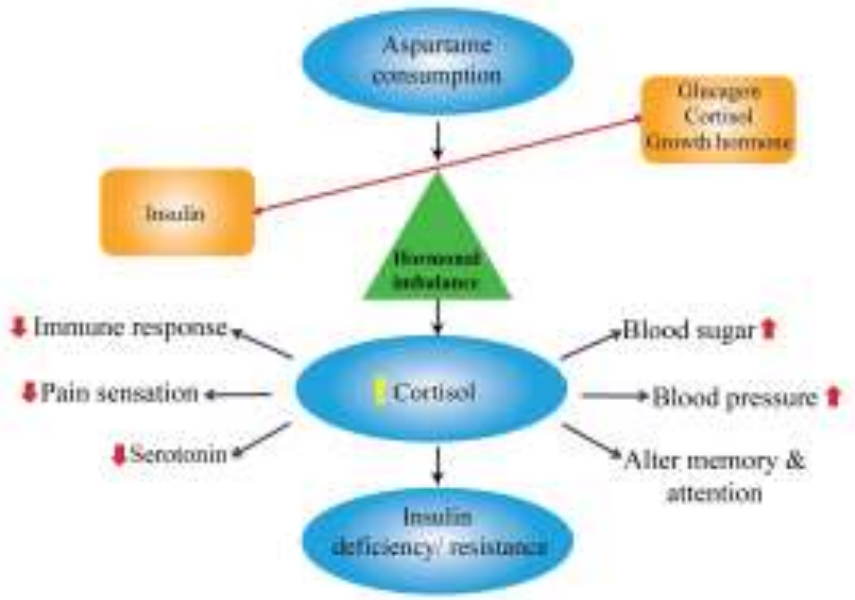

Figure 3: The link between aspartame and cortisol. **A)** Aspartame may act as a chemical stressor and its intake may lead to hormonal imbalance and produce excess cortisol; this may induce insulin resistance or deficiency, and result in increased blood sugar, increase blood pressure, decrease immune response, decrease serotonin and pain sensation and impaired memory and mental attention.

B

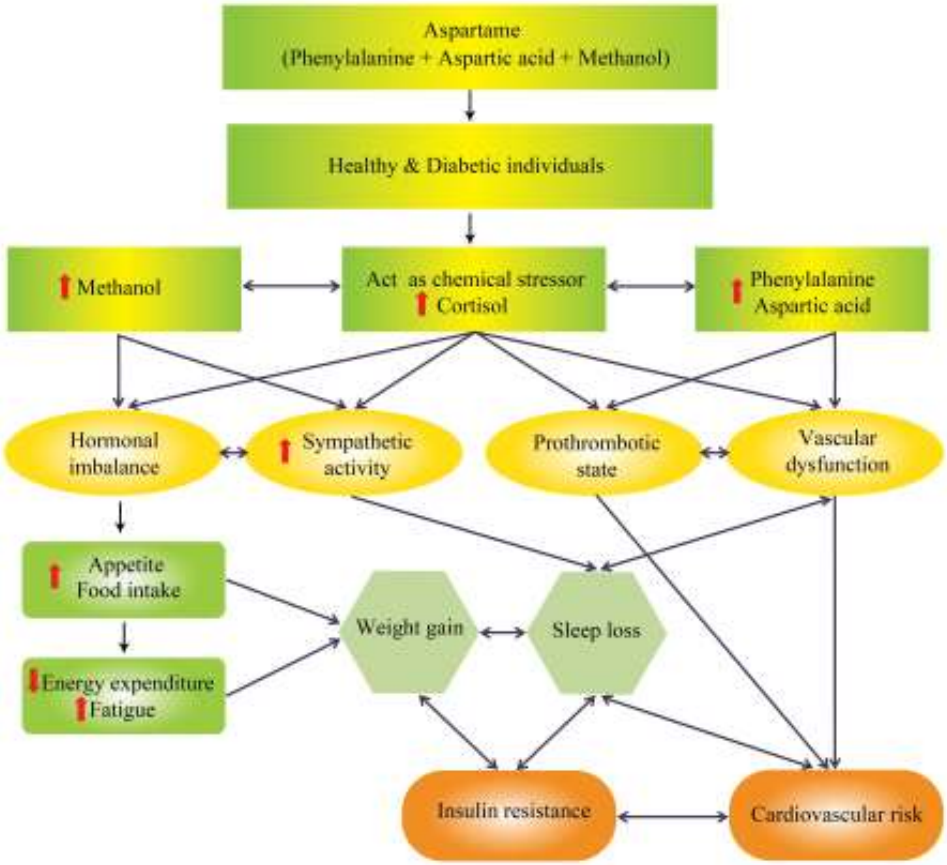

Figure 3: The link between aspartame and cortisol **B)** Increased cortisol or aspartame component, methanol, may lead to hormonal imbalance (increase appetite and food intake, decrease energy expenditure and increase fatigue) and increase sympathetic activity (result in sleep loss) may lead to weight gain, insulin resistance and increase cardiovascular risk. In addition, increased cortisol or aspartame component: phenylalanine and aspartic acid, may affect platelet function, result into prothrobmbic state, vascular dysfunction and increase cardiovascular risk.

Insulin resistance is a state of impaired biological response to normal or elevated serum insulin concentrations[79] and occurs when the body does not respond properly to insulin. Insulin resistance may also be the cause of abnormally high blood glucose levels in T2D[80] due to (a) reduced early insulin secretory response to oral glucose, (b) decreased glucose-sensing ability of the cell, (c) reduced the ability of the cell to compensate for the degree of insulin resistance.

Hypercortisolism and its other complications

Augmented cortisol may also increase sympathetic activity, result in sleep loss; a risk factor for weight gain, insulin resistance, [81] and cardiovascular risk [82] (see Figure 3A and B). Aspartame ingestion result in sympathetic dominance with loss of vagal tone and impaired cardiac function in rats[83, 84]. Mostly Hypercortisolism is associated with central obesity, insulin resistance, dyslipidemia, and alterations in clotting and platelet function[85] (see Figure 3A and B). The duration of cortisol excess correlates with increases the synthesis of several coagulation factors, stimulating endothelial production of von Willebrand factor and concomitantly increasing factor VIII [86] and may also enhance platelet and reduce plasma fibrinolytic capacity[87, 88]. Increased cortisol or aspartame component phenylalanine after aspartame usage may affect platelet function and both fibrin formation and platelet activation in an animal model were found to be to changed fibrin packaging by aspartame administration[89]. Pathological functioning of both platelets and fibrin, closely associated with hypercoagulability, is known to be a hallmark of T2D, and therefore aspartame usage would add to this pathological hypercoaguability in T2D and also in all other inflammatory conditions.

Cortisol may influence the insulin receptor by (a) decreasing binding affinity and receptor number[90], (b) decreasing binding affinity without decreasing numbers[91], (c) increasing receptor number without affecting affinity [92] or (d) having no effect on receptor affinity or number[93]. Insulin receptors are made up of 2 α and 2 β glycoprotein subunits connected by disulphide bonds and are situated in the cell membrane[94] (Figure 4B). Insulin binds to the extracellular α subunit, causing a conformational change, allowing ATP to bind to the intracellular component of the β subunit [79]. ATP binding in turn activates phosphorylation of the β subunit convening tyrosine kinase activity. This enables tyrosine phosphorylation of intracellular substrate proteins known as insulin responsive substrates (IRS) (Figure 4B). The phosphorylated IRS proteins bind with enzymes such as phosphatidylinositol 3-kinase (PI 3-kinase). The PI 3-kinase acts via serine and threonine kinases such as Akt/protein kinase B (PKB), protein kinase C (PKC) and PI dependent protein kinases 1& 2 (PIPD 1 and 2). The PI 3-kinase mediate insulin's metabolic effects [94] by translocation of glucose transporter proteins (GLUT), synthesis of glycogen, lipid and protein, anti-lipolysis and hepatic gluconeogenesis [79] (Figure 4B). Cortisol may cause insulin resistance by decreasing transcription of insulin IRS-1/ IRS-2 in skeletal muscle[95], adipose tissue [96] and liver[97]. Excess cortisol may act as an insulin antagonist in the insulin resistant condition. Hence excess cortisol after chronic aspartame consumption may promote to

insulin resistance, however the particular mechanism has to be explored further with more scientific studies.

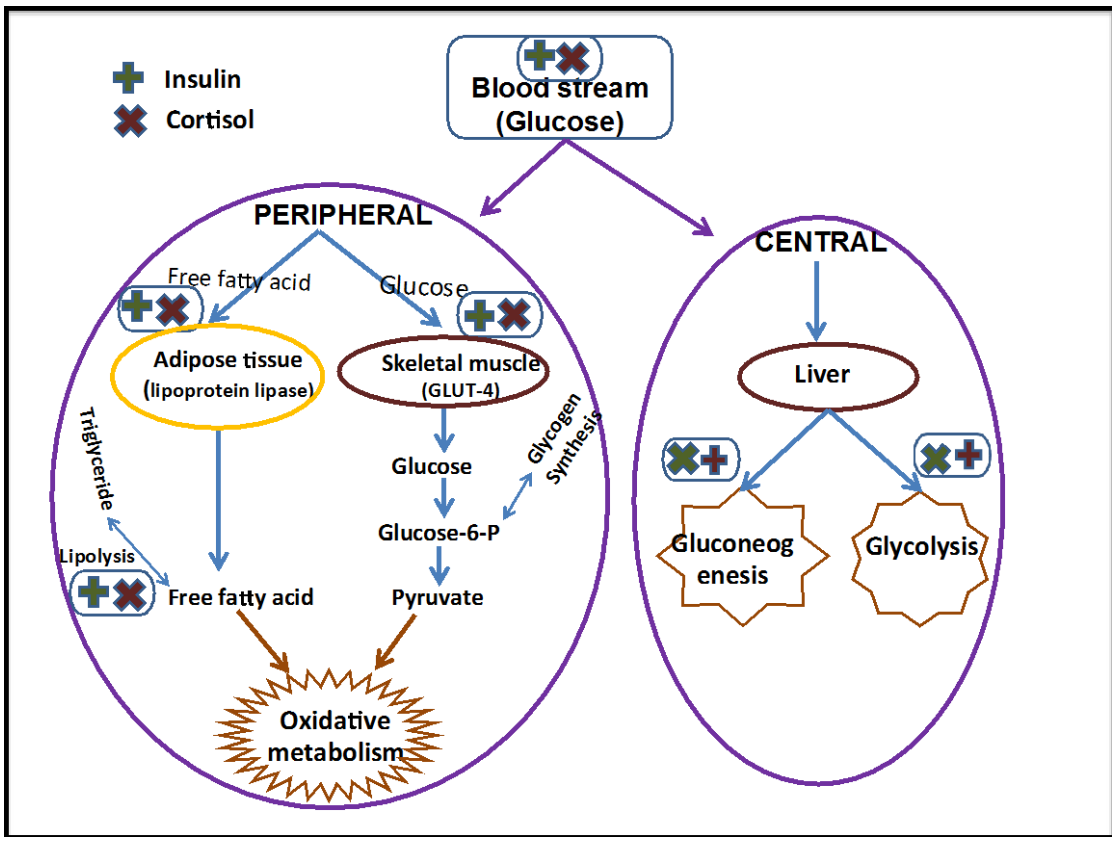

Figure 4A: Insulin and cortisol on peripheral and central glucose uptake. The GLUT 4 is expressed principally in skeletal muscle and lipoprotein lipase principally in adipose tissue. Actions of cortisol (brown color) and insulin (green color) are shown either as stimulate (+) or inhibit (×).The major effects of cortisol may be to reduce translocation of GLUT 4 to the cell surface and enhance lipolysis, thereby increasing free fatty acid competition with pyruvate for mitochondrial oxidative metabolism. In liver, insulin and glucocorticoids oppose each other's actions, particularly on gluconeogenesis and oxidative glycolysis.

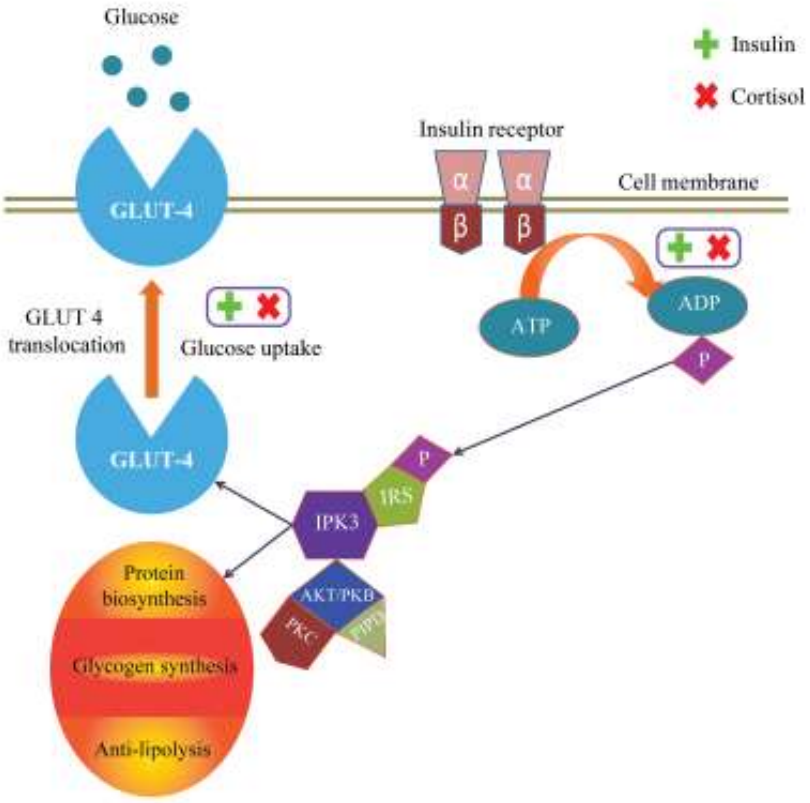

Figure 4B: Insulin and cortisol on insulin receptor (adapted from [79]). Insulin receptors are made up of 2α and 2β glycoprotein. Insulin binds to the extracellular α subunit, subsequent conformational change, allowing ATP to bind to the intracellular β subunit, phosphorylation of the β subunit convening tyrosine kinase activity, and this phosphorylation of insulin responsive substrates (IRS), The Phosphorylated IRS proteins bind with enzymes phosphatidylinositol 3-kinase (PI 3-kinase). The PI 3-kinase acts via Akt/protein kinase B (PKB), protein kinase C (PKC) and PI dependent protein kinases 1& 2 (PIPD 1&2). The PI 3-kinase mediate further insulin's metabolic effects by translocation of glucose transporter proteins (GLUT), synthesis of glycogen, lipid and protein, anti-lipolysis Actions of cortisol (brown color) and insulin (green color) are shown either as stimulate (**+**) or inhibit (**×**) and hepatic gluconeogenesis.

Cortisol also exerts bi-phasic regulation of inflammation in humans and either suppresses or stimulates the inflammatory response in a concentration and time-dependent manner[98]. It is unclear if aspartame consumption causing cortisol production has a pro-inflammatory or anti-inflammatory action.

Neurotransmitter alterations within brain to insulin resistance

The CNS regulates the peripheral metabolism, including energy expenditure, glucose and lipid metabolism, through changes in autonomic sympathetic, parasympathetic, and hormonal outputs[99]. Any aspartame dose consumed by humans will elevate brain phenylalanine much more than it elevates tyrosine, since the human liver converts phenylalanine to tyrosine relatively slowly than in rats[100]. Phenylalanine, rather than tyrosine is the amino acid that is known to be associated with suppression of brain catecholamine synthesis[101] . Aspartame (0.625-45mg/kg) consumption may exert a dose-dependent inhibition of brain serotonin, noradrenaline, and dopamine[38] that may result in a changed neurological function.

Phenylalanine, an aspartame component, competes with tryptophan, the serotonin precursor, for the same channel (NAAT) through the blood-brain barrier[26]. Phenylalanine, penetrates the brain and suppresses serotonin levels [26]. Large doses of phenylalanine can block important neurotransmitters including serotonin, which helps to control sensations of satiety. Serotonin regulates the appetite mechanism and converts into melatonin to induce sleep and serotonin deficiencies can cause depression, upset the appetite mechanism and lead to weight gain [101]. Serotonin may also play a role in glucose homeostasis[102]. The central serotonin 2C receptors in the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of hypothalamus regulate energy and glucose homeostasis[103-105]. The arcuate POMC neurons respond to circulating glucose, and if the KATP channels present in POMC neurons are blocked by a compound such as phenylalanine, may result in impaired glucose tolerance[99, 106]. POMC neurons are also involved in the control of lipid metabolism[107].

People with low levels of serotonin are often compelled to consume more sugar in a bid to increase serotonin production and this often results in a sugar addiction[108], which in turn can lead to insulin resistance (high levels of insulin cause receptors for insulin to shut down by means of ‘down-regulation)[109]. Aspartame consumption in both higher doses [16] and safety doses [110, 111] were shown to induce oxidative stress in the hypothalamus, leading to neuronal death (apoptosis). The glucose regulatory role of the hypothalamus would thus be impaired. Recent research has targeted the serotonin 2C receptors for the treatment of

Diabetes /obesity[112]. The activation of this receptor reduces elevated insulin levels and improves glucose tolerance and insulin sensitivity in both genetically obese mice and in mice with diet-induced obesity[113].

Oxidative stress to insulin resistance

An imbalance between pro-oxidants and anti-oxidants determine oxidative stress and cause cellular disruption and damage[114]. Aspartame induces excess free radical production, in particular, reactive oxygen species (ROS) and reactive nitrogen species (RNS). These free radicals result in systemic oxidative stress[23] such as in blood cells[50, 89, 115-117], brain cells[16, 110, 111, 118, 119], liver and kidney cells[20, 22, 120], heart cells [83, 84] and immune organs[15, 121-123] (Figure 5)**.**

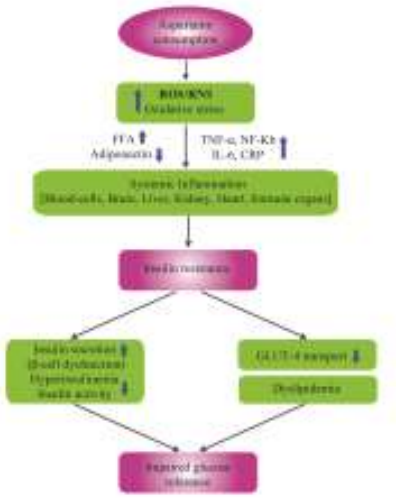

Figure 5: Aspartame usage may result in systemic inflammation and lead to insulin resistance. Aspartame consumption produces excess free radicals (ROS/RNS) production; result in oxidative stress and can trigger pro-inflammatory factor (TNF-α, NF-Kb, IL-6, CRP, FFA), or subsiding adiponectin, lead to systemic inflammation which may result in insulin resistance or impaired glucose transport. [Tumor necrosis factor (TNF-α), nuclear factor kappa B (NF-kβ), C-reactive protein (CRP), Free fatty acid (FFA)].

Systemic oxidative stress is associated with insulin resistance[124]. Oxidative activity among diabetes patients [125] contributes to both the onset and the progression of diabetes as well

as its late complications[126]. Oxidative stress increases with fat accumulation[127]. Oxidative stress may also lead to insulin resistance by stimulating the expression of several pro-inflammatory cytokines[128]. The particular link between oxidative stress and impaired insulin signaling is not completely understood, but several mechanisms have been proposed. ROS/RNS may impair insulin signaling[129-131] by (a) inducing IRS serine/threonine phosphorylation, (b) upsetting cellular redistribution of insulin signaling components, (c) declining GLUT4 gene transcription or (d) altering mitochondrial activity.

ROS can trigger signal transduction pathways, primarily through nuclear factor κB (NFκB), promoting the production of tumor necrosis factor α (TNFα) [132]and increasing the production of pro-inflammatory cytokines, IL-6 [133] and C-reactive protein [128]. Inflammation is recognized as a manifestation of oxidative stress and is important in the development and progression of diabetic complications [134, 135]Increased oxidative stress may cause insulin resistance by inhibiting insulin signals and deregulating adiponectin [127, 136] and other adipocyte-derived factors such as TNF-α[137], leptin [138] and free fatty acids (FFAs) [139](Figure 5)**.** Hence, systemic oxidative stress induced by aspartame usage may exacerbate insulin resistance and impaired glucose tolerance and may increase complications in T2D (Figure 5).

In summary, aspartame usage by T2D may lead to insulin deficiency or resistance by (a) alteration of food habit may lead to weight gain, (b) acting as chemical stressor by increasing plasma cortisol level,(c) inducing excess free radical production, result in systemic oxidative stress, (d) alteration of gut microbes, (e) disrupt neurotransmitter or NMDA receptor [N methyl D-aspartate (NMDA)], finally result in impaired glucose tolerance and may increase complications in diabetic patients; see Figure 6.

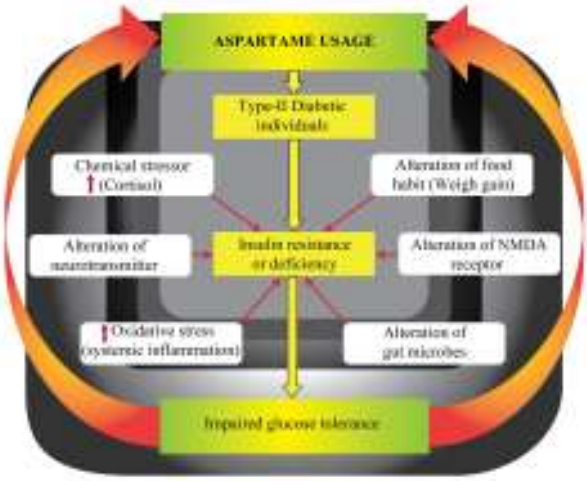

Figure 6: Aspartame usage to insulin resistance. Aspartame usage by type-II diabetic individuals may lead to insulin deficiency or resistance by (a)alteration of food habit (or weight gain), (b) increase cortisol, (c) systemic oxidative stress, (d)alteration of gut microbes, (e) disrupt neurotransmitter or NMDA receptor [N-methyl D-aspartate (NMDA)], and finally result in impaired glucose tolerance.

Limitation and Conclusion

The benefit of aspartame usage as part of regarding weight management and blood glucose regulation in T2D has not been confirmed. To the contrary, many studies link adverse outcomes to aspartame consumption and various systems that are important to diabetic individuals. There are limitations to this review. In particular, data from human studies are limited especially the lack of good quality study design and small sample sizes. In addition, self-reported consumption has not been validated as an accurate measure of aspartame consumption. Unfortunately, results from animal data may not be directly transferable or applicable to human.

We conclude that aspartame use in T2D, may lead to weight gain, rather than weight loss. Aspartame consumption may furthermore act as a chemical stressor, increasing cortisol levels, which interfere with insulin pathways. Moreover, aspartame consumption may induce

systemic oxidative stress by producing excess free radicals, leading to inflammation that may exacerbate T2D complications.

More research is required that provides evidence and raise concerns that use of aspartame in T2D is a challenge, and we suggest that aspartame consumption regulations should be revisited and international guidelines reviewed to add further to the already challenged health burden of T2D.

Disclosure

The author does not have any conflict of interest to declare.

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