1   **Insulin Resistance Syndrome- the sensitive IRS**

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10   **Abstract**

11   Insulin resistance is a prominent pathophysiologic syndrome in a plethora of metabolic

12   disorders including obesity, prediabetes, type 2 Diabetes Mellitus (Ten et al., 2007), impaired

13   glucose tolerance, dyslipidemia, polycystic ovary syndrome and hypercoagulability (Smith &

14   LeRoith, 2004). It is strongly associated with obstructive sleep apnea, hypoventilation syndrome,

15   pancreatitis, nonalcoholic fatty liver disease, steatohepatitis, cirrhosis, gall bladder disease,

16   multiple cancers (breasts, uterus, cervix prostate, kidney, colon, esophagus, pancreas and liver),

17   stroke, cataracts, coronary heart disease, and hypertension. It is also associated with causation of

18   abnormal menses, infertility, polycystic ovary syndrome, osteoarthritis, phlebitis and other

19   venous diseases.

20   Insulin resistance is thought to be caused by intrinsic and extrinsic factors that contribute to its

21   development. Once present, insulin resistance affects the metabolism, behavior, physical

22   appearance and has lasting effects. This paper will review the latest evidence in development of

23   insulin resistance, its pathogenesis and manifestation and its relation to other conditions. The

24   final aim is to raise awareness of its role on diet, metabolic, genetics and microbiome.

25   **Keywords**: insulin resistance, diet, exercise, microbiome, metabolic disorders

26   **Insulin resistance pathogenesis**

27   The term insulin resistance implies excess production of insulin as a response to

28   triggering factors which makes the receptors overworked and overused to it therefore more

29   insulin is needed to achieve needed effect. Insulin resistance was first described in 1936 to

30   illustrate a metabolic disturbance showing impaired cellular responsiveness to insulin signaling

31   in insulin dependent tissues such as skeletal muscle, liver, and adipose tissue (Bermudez et al.,

32   2016). Studies point to alarming projections for the future with an estimated prevalence of 33 %

33   of the adults in USA alone (Bermudez et al., 2016). Insulin resistance syndrome (IRS) has a

34   domino effect mostly associated with the liver, muscle, adipose tissue and endothelium. Insulin

35   causes a powerful shift of the metabolism towards hepatic triglyceride production, cholesterol

36   synthesis, followed by transport and tissue accumulation of the lipids produced. However, the

37   continued flow of insulin production at the level of the pancreatic beta cell leads to eventual

38   exhaustion of the insulin production and secretion apparatus, eventually causing type 2 diabetes

39   mellitus (T2DM). The ongoing hyperinsulinemia leads to significant dyslipidemia and vascular

40   inflammation, producing cardiovascular disease (Lopez-Candales, Hernández Burgos,

41   Hernandez-Suarez, & Harris, 2017).

42   The deposition of excess glucose and end products glucose of metabolism in sensitive

43   tissues such as the brain, is believed to have a causative role in the development of Alzheimer's

44   disease, (also classified as a type of diabetes) (de la Monte & Wands, 2008). Insulin inhibits

45   gluconeogenesis and promotes glycogen production and once the glycogen stores are maximized,

46   insulin stimulates the conversion of glucose into fatty acids. When carbohydrates are abundantly

47   present, the body enters in a process of producing more and more insulin to regulate the glucose

48   metabolism which may cause drop in blood glucose and ingestion of more carbohydrates to

49   counteract effects of reactive hypoglycemia therefore starting a vicious cycle. This is because of

50   the metabolic consequences of insulin excess in the presence of high blood sugar levels.

51   Intrinsic behaviors such as compulsive eating and stress eating have been associated with

52   insulin resistance. Overeating is one of the major causative factors that induces low grade

53   inflammation secondary to activation of various transcriptional mediated molecular a metabolic

54   pathways which happen due to elevated glucose and lipids in blood stream (Paniagua, 2016).

55   Other intrinsic factors include metabolism, genetics, microbiomes behavior and pathologic

56   conditions. The extrinsic pathogenic factors for insulin resistance include diet, physical activity,

57   social pressures, toxins and medications. In the latter category, meds such as statins, thiazides,

58   beta blockers, antiretroviral, steroids, antiestrogens, chemotherapy and antirejection drugs are

59   known to affect glucose metabolism (Bays, 2011). Once, IRS is developed, it increases the

60   oxidative stress in b cells of pancreatic islets and peripheral tissues. To counter these processes,

61   the best approach is to prevent the pathogenies of IRS thru ameliorating the incidences of

62   inflammatory responses (Rehman & Hamid Akash, 2016).

Metabolic syndrome

64   Metabolic syndrome (MetS) is considered a IRS surrogate (Singh et al., 2012) and

65   represents a clinical diagnostic entity identifying the individuals at risk with cardiovascular

66   morbidity linked to IR (Wilcox, 2005). MetS is a cluster of five condition with three of them

67   confirming diagnosis. The five criteria for diagnosis are abdominal obesity,

68   hypertriglyceridemia, low HDL-C, hypertension and elevated fasting glucose. Regardless of

69   various names and definitions, it is estimated that nearly 100 million Americans or about 30. 5 %

70   have MetS, mostly undiagnosed. IRS is suggested to be a major factor linking physical

71   inactivity and MetS (Roberts, Hevener, & Barnard, 2013). Together, increased consumption of

72   refined sugars, saturated fats, and increased calorie intake, linearly correlate with increased

73   prevalence of obesity, diabetes and other components of metabolic syndrome (Siegfried, Shiho,

74   & Kahn, 2016).

75   **Genetics and insulin resistance**

76   The most common genetic obesity condition resistant to weight loss are the Prader Willi

77   syndrome occurring in one out of 20,000 births followed by rarer conditions such as the Bardet

78   Biedl syndrome, the Cohen and Ayazi syndrome (Gunay-Aygun, Cassidy, & Nicholls, 1997).

79   The recently discovered, non-syndromic genetic obesity patterns have the opposite

80   characteristics. Variations in ADIPOQ are associated with obesity, type 2 diabetes (T2DM) and

81   related phenotypes in several populations including Asian populations (Siitonen et al., 2011).

82   They result in a reduction in adiponectin, an adipocyte hormone that reduces inflammation,

83   dyslipidemia and insulin resistance. On the other hand, liver also has an important role in

84   nutrition metabolism thru regulation via production of the hepatokine fibroblast growth factor 21

85   (FGF21), which significantly suppresses consumption of simple sugars, but not complex

86   carbohydrates, proteins, or lipids. Von Holstein et al, 2016 believe that the liver regulates the

87   intake of certain micronutrients by increasing endocrine satiety meaning that literally suppresses

88   the intake of sugars since its elevated numbers positively correlate with BMI, waist

89   circumference (WC), fat mass and central adiposity (Chu et al., 2013; von Holstein-Rathlou et

90   al., 2016). Chu et al, 2013 performed a large study of a genome-wide meta-analysis of 33355

91   male and female participants of European ancestry in DietGen consortium consisting of three

92   large population-based studies, investigating the genetics of dietary intake and nutrition and

93   found results that demonstrate associations with macronutrient intake at genome-wide

94   significance (Chu et al., 2013; Heianza et al., 2016).

95   **Microbiome contribution**

96   This is an emerging field and we are now recognizing the role that the bacterial flora has

97   in contributing to our energy harvest and to modifying our diet and behavior. The potential

98   importance of gut microbiota was recognized more than 1000 years ago in China where fecal

99   transplants known as "yellow soup" were used to treat gastrointestinal disorders. Scientific

100   community agrees that not all the bacteria are harmful and shifting the gut bacteria can be proven

101   to be useful (Siegfried et al., 2016). Backhed et al, 2004 connected the role of microbiota in the

102   pathogenesis of obesity and regulation of fat storage (Backhed et al., 2004). Humans have a

103   specific bacterial flora that sets in by very young age but can be modified over the years by diet,

104   antibiotics, xenobiotics, environment, stress and other factors that continuously change its shape

105   and structure (Riaz Rajoka et al., 2017; Shen, 2017; Siegfried et al., 2016; Tidjani Alou, Lagier,

106   & Raoult, 2016). Colonization of the neonatal intestine is critical for neonatal development and

107   has a long term impact on overall health (Azad, Moossavi, Owora, & Sepehri, 2017). Early

108   antibiotic exposure has been associated with trends of obesity later on in life secondary to lower

109   bacterial diversity (Azad et al., 2017). The two major gut phyla are firmicutes and bacteroidetes.

110   The bacterial diversity of species within these groups has also been shown to be a factor for

111   obesity. Obese animals and humans tend to have less diverse city with a higher F/B ratio. After

112   temporary insult, eventually the microbiome could change back to initial composition (David et

113   al., 2014). The dysbiosis in the intestine has also been blamed on increased shedding of

114   lipopolysaccharide (LPS), an endotoxic molecule from the outer membrane of gram negative

115   bacteria. To the contrary, microbial transfer from one individual to another increases diversity

116   and leads to weight loss. Moreover, microbiota can produce and modify human metabolites such

117   as bile acids that have the potential to modulate host metabolism, influence and affect behavioral

118   and neural functions. The microbiome can also influence the immune system and the integrity of

119   intestinal epithelium allowing endotoxins to enter the blood stream resulting in IRS along with

120   other immune mediator disorders (Siegfried et al., 2016). An article by Zeevi et al, in non-

121   diabetic overweight individuals (Zeevi et al.) included 800 subjects with continuously monitored

122   week-long glucose levels of glycemic responses and microbiome changes to 46,898 meals.

123   Lastly, it is hypothesized that metformin exerts antio-besity effect via gut microbiome

124   modulation in prediabetics as affects the growth of certain bacteria in microbiome composition.

125   Metformin is widely use in prediabetes, IRS and PCOS as all are related.

126   **Fat effect**

127   IRS is strongly linked to fatty acid deposition with the visceral adipose tissue. Adipokines

128   such as leptin, adiponectin, resistin, omentin, visfatin, vaspin and apelin are released from fat

129   tissue to the general circulation, often with adverse effect. Fat storages are known major forces

130   behind T2DM. Lipid induces adipose tissue inflammation that relates with certain defects in

131   adipocytes (Bhattacharya & Mukherjee, 2016). There have been conflicting studies in this area

132   (Chowdhury et al., 2013; Hoenselaar, 2012; Siri-Tarino, Sun, Hu, & Krauss, 2010) . For

133   example, Siri Tarino performed a meta-analysis in 2010 of 347,747 subjects (Siri-Tarino et al.,

134   2010). They found "no evidence for CVD risk with saturated fat ". In 2014 Chaudhry performed

135   a meta-analysis of 512,420 subjects and discovered no associations between total saturated fatty

136   acids and coronary risk (Chowdhury et al., 2013). In 2013, Ramsden reviewed both the Sidney

137   Heart Study and the Minnesota Coronary Experiment and concluded that both had overestimated

138   the benefits of replacing saturated fat with vegetable oils (Ramsden et al., 2013). These studies

139   and others led Ludwig (Ludwig, 2016) to state that there had been a massive public health failure

140   regarding the concept of saturated fat and cardiovascular disease. Nonetheless, Wang recently

141   reported data from the NHS and HPFS studies including data with more than 3.5 million patient

142   years. They found that replacement of saturated and trans fatty acids with unsaturated fats

143   reduced total mortality (J. Wang et al., 2013).

144   **Other factors**

145   The reduction in physical activity that has occurred in our society after World War II has

146   had a dramatic impact on insulin sensitivity of the general population. Sedentary behavior and

147   the under use of skeletal muscle leads to impairment of glucose uptake via the GLUT4

148   transporter (Richter & Hargreaves, 2013). Regarding the toxins, chemical additives have been

149   used as flavor, color and aroma enhancers which makes certain foods irresistible and more

150   addictive. Other toxins such as pesticides and plasticizers and the persistent exposure to them

151   undoubtedly have an impact on hormonal regulation including insulin resistance and other

152   metabolic disorders (Ruzzin et al., 2010).

153   **IR manifestations and diagnosis methods**

154   *Anthropometrics and physical exam*

155   Excess insulin has a potent proliferative effect on epidermal keratinocyte and dermal

156   fibroblasts. These changes result in arochordons, acanthosis nigrans, androgenetic alopecia, acne

157   and hirsutism to name a few (González-Saldivar, Ocampo-Candiani, Gómez-Flores, Rodríguez-

158   Gutiérrez, & González-González, 2017). By diagnosing these manifestations timely and referring

159   patient for further diagnosis and treatment, there can be a decrease in the obesity and diabetes

160   burden and patients may have a better quality of life (González-Saldivar et al., 2017). The

161   characteristic appearance of acanthosis nigrans begins with a darkening of skin at the base of the

162   neck often seen as a ring-like presentation that surrounds the entire neck. Excess insulin has high

163   affinity to other tyrosine kinase receptors causing epidermal growth and fibroblasts receptors.

164   Clinical signs also include truncal obesity attributed to the insulin driven deposition of fat in the

165   visceral adipose tissue (VAT) depot. This is best estimated by a measurement of the waist

166   circumference (WC) and noted by increased hip to waist ratio. All fat was initially thought of

167   simply as an energy reservoir but now is considered a metabolically active endocrine organ.

168   *Metabolic testing*

169   A high sensitivity C-reactive protein (hsCRP), HbA1c and fasting insulin levels are

170   diagnostics factors along with nuclear magnetic resonance (NMR) lipid profile and repeated

171   urine microalbumin. The presence of elevated CRP (synthesized in liver) has been shown to

172   positively correlate with BMI, waist circumference and insulin resistance (Fonseca & de Oliveira

173   Izar, 2016). NMR spectroscopy informs about the atherogenicity of lipoprotein profile thru a LP-

174   IR score (Colhoun et al., 2002). Koskinen measured LDL particle number in 1,400 healthy

175   subjects in which, those with the highest LDL particle number were 2.8 times likelier to have

176   metabolic syndrome than those with the lowest level of LDL particles (Koskinen et al.). The LP-

177   IR Score was developed using HOMA-IR in 4972 nondiabetic subjects and verified using

178   glucose disposal rates measured during a hyper-insulinemic–euglycemic clamp and is significant

179   over 50 (Shalaurova, Connelly, Garvey, & Otvos, 2014). The homeostatic model assessment

180   (HOMA) is a mathematical method used to quantify insulin resistance and beta-cell function

181   with levels of > 2.4 being considered significant, derived from a fasting plasma glucose (FPG)

182   and fasting plasma insulin (FPI) levels. Fasting dyslipidemia and lipid panel provide useful

183   information in regard to IR and metabolic syndrome (Ray et al., 2012). Hyperglycemia alone is a

184   major factor as it is strongly related to prediabetes (Dankner, Chetrit, Shanik, Raz, & Roth;

185   Selvin et al., 2010). Oral glucose testing (OGTT) is superior testing that needs to be incorporated

186   more as detects diabetes more efficiently than fasting glucose (FPG) as it recognizes altered post-

187   prandial metabolism. This test cannot be substituted with AIC testing as they are not equivalent

188   tests (Bartoli, Fra, & Schianca).
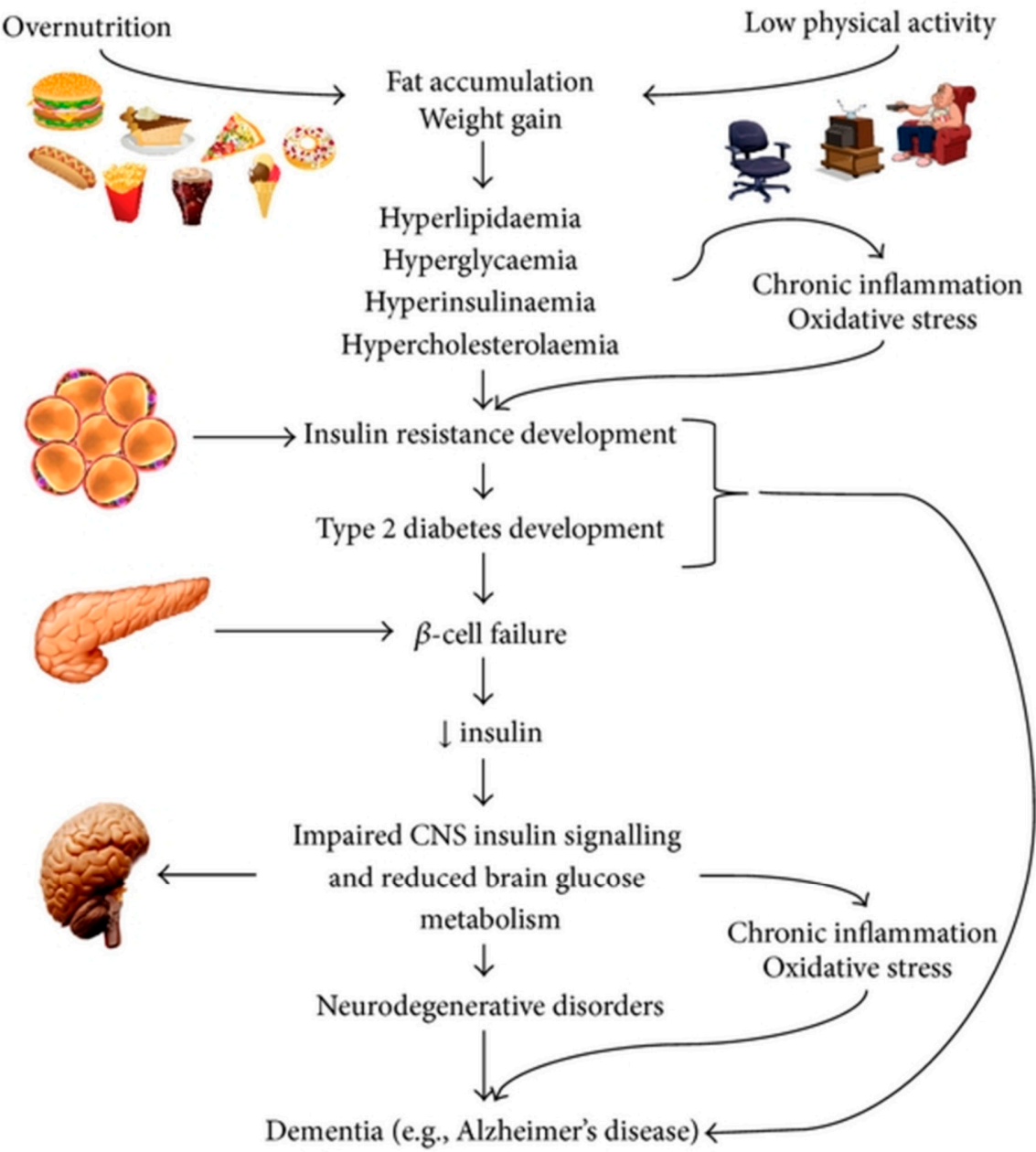
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190   Fig. 1 Conditions associated with IR. Adapted with permission from (Verdile et al., 2015)

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Intervening factors in Insulin resistance

Dietary modification

The dietary goals to modify insulin resistance are moderate caloric restriction and macronutrient substitution based on the metabolic findings. The patient must achieve a dietary pattern that is sustainable over the long term and is feasible to adhere to. The purpose of achieving a sufficient caloric restriction beside losing weight is also for the health benefits as numerous studies have demonstrated that a weight loss as little as 5% has been effective in reducing IR and preventing T2DM (Tuomilehto et al., 2001). A general principle is to lower fat intake and limit carbohydrates to those of low glycemic control and maintain protein intake with respect to calorie moderation. Fiber intake also plays a factor in maintaining weight. Furthermore, individual metabolic variations exist as well as specific genomic variations, microbiome heterogeneity, culture, geography, agriculture, etc. In 2011, Salas Salvadó et al published an analysis of food nutrients and dietary patterns for the prevention of diabetes mellitus (Salas-Salvado, Martinez-Gonzalez, Bullo, & Ros, 2011). Foods such as sugar rich beverages, fruit juices, meats, hydrogenated oils/margarine and eggs; nutrients such as saturated fatty and trans fatty acids and dietary patterns such as high glycemic index and Western diet all increased risk of T2DM. On the other hand, foods such as whole grains, coffee and tea, low-fat milk and dairy, moderate alcohol, fruits and vegetables, nuts; nutrients such as fiber, unsaturated fatty acids, antioxidants, magnesium and dietary patterns such as low-glycemic index, Mediterranean and a low fat prudent diet all lowered the risk of T2DM. They additionally stated a low glycemic index dietary pattern that was high in fiber, magnesium and antioxidant was associated with reduced oxidation, inflammation and IRS. On the other hand, a high glycemic index dietary pattern high in saturated and trans increased oxidation, inflammation and IR.

215   Weickert, 2012 looked at the concept of nutritional modulation of insulin resistance in 2012

216   (Weickert, 2012). He described dietary patterns in terms of insulin sensitive or insulin resistant.

217   With similarity to Salas Salvadó, he found that poly and monounsaturates, low glycemic index,

218   high fiber diets favored insulin sensitivity. Whereas, saturated and trans fatty acids, animal

219   protein and high glycemic index foods favored IRS.

Diet Modulation Options: Macronutrients

Choosing fats wisely

222   Thru manipulation of nutrition science (Kearns, Schmidt, & Glantz, 2016) decreasing fat

223   and raising carbohydrates was promoted resulting in 1992 food pyramid. Lately many new food

224   pyramids have come to light. There is little doubt that a reduction in saturated fat improves

225   insulin sensitivity. It is fair to state that high saturated fat diets raise LDL cholesterol whereas

226   high mono and polyunsaturated fat diets lower it which in return lowers CVD. In the Finnish

227   Hospital study and Los Angeles study, use of dietary polyunsaturated fat lowered cholesterol

228   significantly which translated to a reduction in cardiovascular disease (Siri-Tarino et al., 2010).

229   Replacement of saturated fats by polyunsaturated was shown to be beneficial in a pool analysis

230   of 11 major population cohort studies, with 344,696 participants in which saturated fat was

231   replaced by polyunsaturates reduced heart disease. But when the saturated fats were replaced by

232   carbohydrates, the risk of coronary disease increased (Jakobsen et al., 2009).

Balancing carbohydrates

234   A large number of published reports suggest that reduction of carbohydrates is the most

235   appropriate step in modifying a diet for IR. For example, in 2002 Westman demonstrated value

236   in 41 patients on a very low carbohydrate diet (VLCD; < 25 g per day) (Westman, Yancy,

237   Edman, Tomlin, & Perkins, 2002). In 2003, Foster compared VLCD to a low-fat diet in 63

238   patients (Foster et al., 2003). Brehm, Yancy and Stern each conducted randomized clinical trials

239   showing benefit of the VLCD over a low-fat diet (Brehm, Seeley, Daniels, & D'Alessio, 2003;

240   Stern et al., 2004; Yancy, Olsen, Guyton, Bakst, & Westman, 2004). And most recently in 2014,

241   Bazzano, 2014 showed the benefits of a low carbohydrate diet on cardiovascular risk in 148

242   participants studied for 12 months (Bazzano et al., 2014). However, studies have shown that

243   patients regain weight due to lack of structure and lack maintenance with other studies showing

244   that weight gain may occur few years after the initial weight loss.

245   *Calories matter*

246   Sacks et al, 2009 compared four diets of varied carbohydrate content (high, low

247   carbohydrate, high low glycemic index) and quality in 163 overweight adults (Sacks et al.,

248   2009). After 12 weeks, no effect could be demonstrated by the influence of the carbohydrate

249   intake. In the Pounds Lost study, Sacks, Bray and colleagues studied 811 IRS subjects. The

250   subjects were divided into groups that consumed 4 different dietary patterns which consisted of

251   carbohydrates, fat and protein content. At six months each dieter regardless of diet, had lost

252   about 6 kilograms or about 7 % of their body weight and eventually they regained some after 12

253   months. By two years, the weight loss among all groups averaged between 2.9 to 3.6 (p> 0.20).

254   Overall regardless of diets, their insulin levels and lipid related risk factors improved (Sacks et
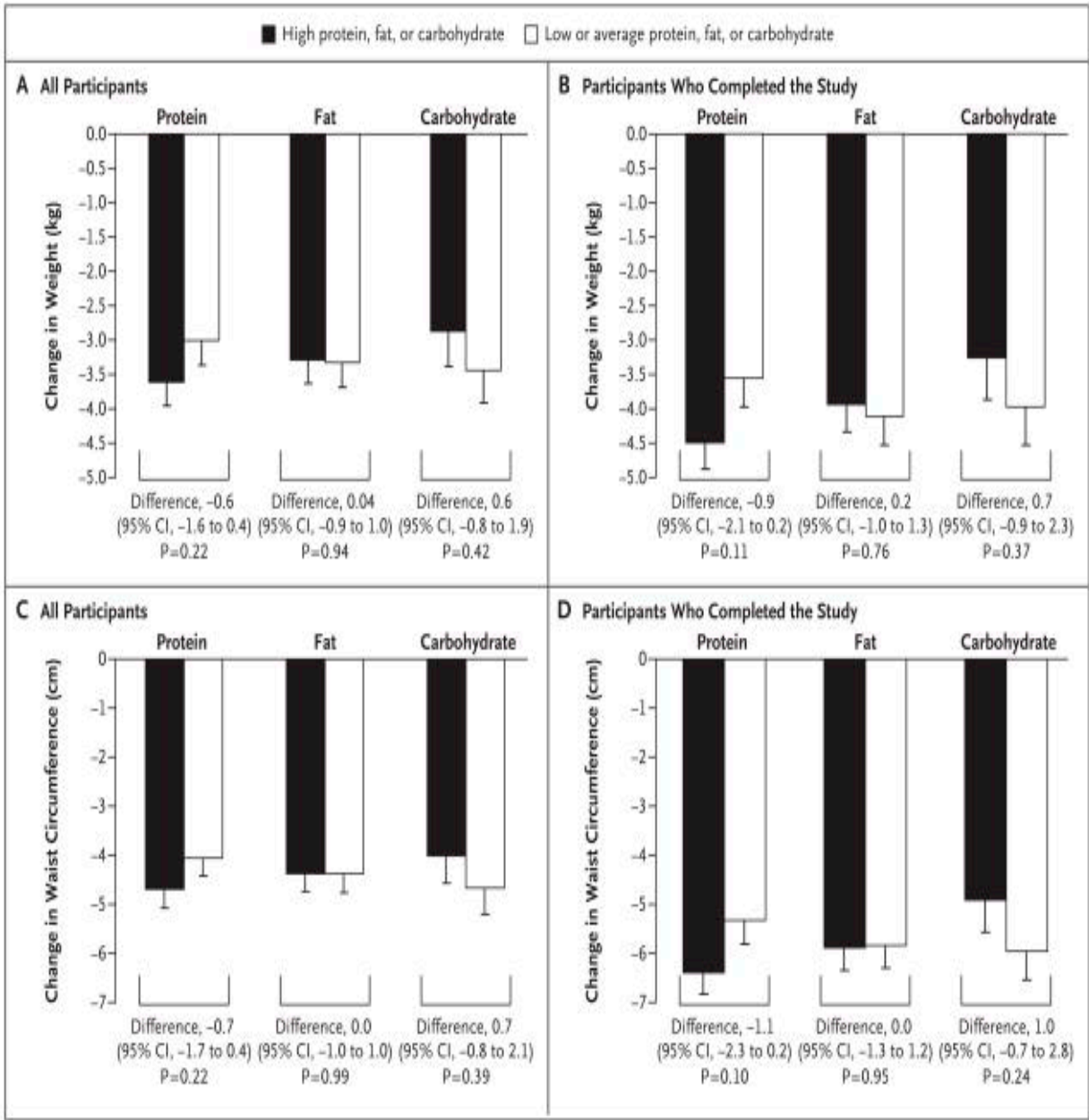
255   al., 2009).

Fig. 2 (Sacks et al., 2009) Reproduced with permission from Massachusetts Medical Society (12/2017)

Maintaining protein intake

Increase intake of protein has been promoted in the past due to the belief to have weight-loss benefits. This diet change had shown to increase satiety, improve blood sugar control, reduce HOMA-IR and preserve lean body mass during weight loss (Cuenca-Sánchez, Navas-Carrillo, & Orenes-Piñero, 2015; J. O. Hill & Peters, 2002) Ley, 2014 examined the type of protein utilized by comparing unprocessed processed and unprocessed red meat to red meat substitutes. Avoiding animal protein appears to be beneficial for IRS (Ley et al., 2014). The effect of high-protein diets on the modulation of satiety involves multiple metabolic pathways such as induction of complex signals, with peptide hormones being released from the gastrointestinal tract and blood amino acids and derived metabolites being released in the blood. Protein intake also stimulates metabolic hormones that communicate information about energy status to the brain. Long-term ingestion of high amounts of protein seems to decrease food intake, body weight, and body adiposity in many well-documented studies (Cuenca-Sánchez et al., 2015). Long-term consumption of a high-protein diet has been associated with metabolic and clinical problems, such as loss of bone mass and renal dysfunction but evidence is lacking (Cuenca-Sánchez et al., 2015).

Complex Dietary Patterns in IRS

An alternative approach to adjusting macro nutrients in the management of IR is the consideration of dietary patterns which may be beneficial. Examples of these include the DASH diet, the Healthy Eating Index/ Alternative Healthy Index diets and the Mediterranean diet. Appel and colleagues published result of the DASH diet on blood pressure in 1997 showing significant drop in arterial pressure just two weeks on the diet (Appel et al., 1997). The DASH diet reduced fasting insulin but had no effect on fasting glucose or HOMA-IR ($p > 0.8$ for the

283   interaction) (Corsino et al., 2017). Adherence to the Alternative Healthy Index diet showed

284   reversion of metabolic syndrome in individuals with central obesity and elevated triglycerides

285   (Akbaraly et al., 2010). Significant reduction of 72 % in cardiovascular events on the role of a

286   Mediterranean diet in reducing cardiovascular events began in 1998 with the Lyon diet heart

287   study in France. In 2004, Esposito and Giuliano conducted a 3-year trial of a Mediterranean diet

288   in patients with metabolic syndrome in Italy (Esposito, Kastorini, Panagiotakos, & Giugliano,

289   2011). They showed improvement in blood pressure, triglycerides, HDL, glucose, insulin,

290   inflammatory markers and sexual function. They also performed in L arginine test for nitric

291   oxide formation and found improvement after the Mediterranean diet (Esposito et al., 2011). By

292   far the largest and most complete analysis of the Mediterranean diet was performed in Spain by

293   the Predimed study in which over 7000 subjects were enrolled with 3287 completers studied over

294   five years. The subjects were divided into a control group that followed an American Heart

295   Association type low-fat diet. In Predimed, study arm one group followed a Mediterranean diet

296   enhanced by extra-virgin olive oil while the group two subjects followed a Mediterranean diet

297   enhanced by nuts (Estruch et al., 2013). After five years, there was a 30% reduction in

298   cardiovascular events. In later reports the Predimed investigators concluded that Mediterranean

299   diets supplemented with either extra-virgin olive oil or nuts delay the onset of metabolic

300   syndrome and are more likely to cause its reversal (Salas-Salvado et al., 2011; Sureda et al.,

301   2016). Weichert, 2012 has reviewed dietary modification for insulin sensitivity and investigated

302   the effects of modulating the macronutrient composition of isoenergetic diet and published

303   comparing each intervention and its effect on weight loss, insulin resistance, diabetes risk and

304   other effects (Weickert, 2012).

305

Gut Microbiome interventions

The gut microbiota has gained attention as an active game player in development of IR, obesity and cardiovascular disease. Associated are the short chain fatty acids who contribute to the energy harvest from the foods that are eaten. The gut bacteria produce vitamin K, pantothenic acid as well water-soluble vitamins including biotin, nicotinic acid, folates, riboflavin, thiamine, pyridoxine, and cobalamin (M. J. Hill, 1997). They also produce a series of short chain fatty acids, including acetate, propionate, butyrate, TMAO and others. Short chain fatty acids (SCFA) are the primary end-products of fermentation of non-digestible carbohydrates that are absorbed by the body as fuel supplying most of the energy needs for colonocytes and approximately 10% of the total body's energy needs. But these substances also act as signals which impact lipid, glucose and insulin metabolism (Morrison & Preston, 2016). The review from Morrison & Preston, 2016 reveals that SCFA may have an important role during lifetime in protecting the body against deteriorating metabolic control and inflammatory status associated with Western lifestyles. Vijay-Kumar showed that microbial changes, such as antibiotic administration have a role in inducing metabolic syndrome and insulin resistance (Vijay-Kumar et al., 2010). A number of studies have shown the benefit of probiotics on reducing IR. Ruan, 2015 recently performed a meta-analysis on these reports with a total of 614 participants in which the probiotics were favored on HOMA-IR (Ruan et al., 2015). Similar results have been obtained from yogurt consumption, which can be expected to have a probiotic effect. Wang et al, 2013 reviewed Framingham cohorts including 6,526 individuals, comparing non-yogurt consumers, low intake and high intake consumers. Statistically significant improvements in triglycerides, glucose, insulin, systolic blood pressure and HOMA-IR were observed (Wang, Livingston, Fox, Meigs, & Jacques, 2013).

329   Probiotics and Synbiotics

330   While genetics are a nonmodifiable component of human, the microbiome could

331   potentially be modified by lifestyle and symbiotic or probiotic supplementation to manage

332   metabolic diseases (Barengolts, 2016). Consuming probiotics or synbiotics may improve fasting

333   blood glucose. In a metanalysis from Nikbakht et al, 2016, the analysis of the 14 studies showed

334   that multispecies probiotics may have a better impact than single species ones (Nikbakht et al.,

335   2016). Dietary fiber undergoes complete or partial fermentation depending on the kind of fiber

336   and enhances calcium absorption with the possibility to influence microbiome and bone health.

337   Most Americans lack fiber intake. The recommended dose is 14gm/1000 calories (Wallace,

338   Marzorati, Spence, Weaver, & Williamson, 2017).

339   **Micronutrients**

340   *Magnesium*

341   Magnesium intake is also believed to be beneficial to reducing and IR. Wang, 2013

342   studied dietary magnesium in patients with MetS showing risk reduction in the subjects with the

343   highest dietary magnesium intake (J. Wang et al., 2013). In addition, a meta-analysis of 13

344   prospective cohort studies by Dong, 2011 including 536,318 participants and 24,516 cases

345   detected a significant inverse association between magnesium intake and risk of T2DM (relative

346   risk (RR 0.78) (Dong, Xun, He, & Qin, 2011). This association was regardless of geographic

347   region, follow-up length, sex, or family history of T2DM. A significant inverse association was

348   observed in overweight (BMI ≥25 kg/m(2)) but not in normal-weight individuals (BMI <25

349   kg/m(2) (Dong et al., 2011).

350

351   *Vitamin D*

352   An extensive literature exists about vitamin D and IRS. This includes studies on patients

353   with normal glucose tolerance, pre-diabetes and established T2DM. Seida, 2014 performed a

354   meta-analysis of the studies and they were unable to achieve statistical significance (Seida et al.,

355   2014).

356   *Omega 3 Fatty Acids*

357   Supplementation with omega-3 fatty acids or inclusion of foods high in these essential

358   fats has been extensively studied in IRS. The multivariable adjusted risk reduction was recently

359   calculated through a meta-analysis performed by Kim (Kim et al., 2009). In this study the overall

360   effect showed a modest reduction in IR with the consumption of omega-3 fatty acids.

361   *Polyphenols*

362   Polyphenols among others include phenolic acid, flavonoids and stilbenes. Fruit and

363   beverages such as tea and red wine constitute the main sources of polyphenols. Certain

364   polyphenols such as quercetin are found in all plant products (fruit, vegetables, cereals,

365   leguminous plants, fruit juices, tea, wine, infusions, etc), whereas others are specific to particular

366   foods (flavanones in citrus fruit, isoflavones in soya, phlorizin in apples) (Manach, Scalbert,

367   Morand, Remesy, & Jimenez, 2004).

368   Although low in polyphenols, several authors have suggested a benefit in consumption of

369   avocado on IRS and metabolic syndrome. This was studied in detail by Fulgoni, 2013 who

370   compared metabolic syndrome indices in avocado consumers and non-consumers (Fulgoni,

371   Dreher, & Davenport, 2013). They analyzed the NHANES 2001-2008 database and reviewed

372   17,567 subjects. Their study found statistically significant improvements in body weight, BMI,

373   waist circumference and HDL in avocado consumers. Avocados contains good fats and slows

374   insulin release in the body and helps the person to stay full longer.

375   There are at least 17 clinical studies published on the benefit of green tea in metabolic

376   syndrome and IR. Liu, 2013 performed a meta-analysis of these, including 1133 subjects (Liu et

377   al., 2013). They found a net negative change in fasting glucose, fasting insulin, HbA1c, 2-hour

378   glucose and HOMA-IR. However, in their initial analysis they were only able to demonstrate

379   statistical significance in fasting glucose, and HbA1c. The role of cinnamon has been also

380   researched for its glucose lowering properties.

381   A similar review is available on resveratrol, a bioflavonoid antioxidant found in wine and

382   berries. Liu, 2014 performed a meta-analysis of seven studies, two in diabetics and five in non-

383   diabetics. The effect was greater in diabetics, but overall HOMA-IR was reduced significantly by

384   resveratrol (Liu, Zhou, Wang, & Mi, 2014).

385   **Precision Medicine and recommendations**

386   Unquestionable, the Insulin resistance syndrome affects the body as whole medically and
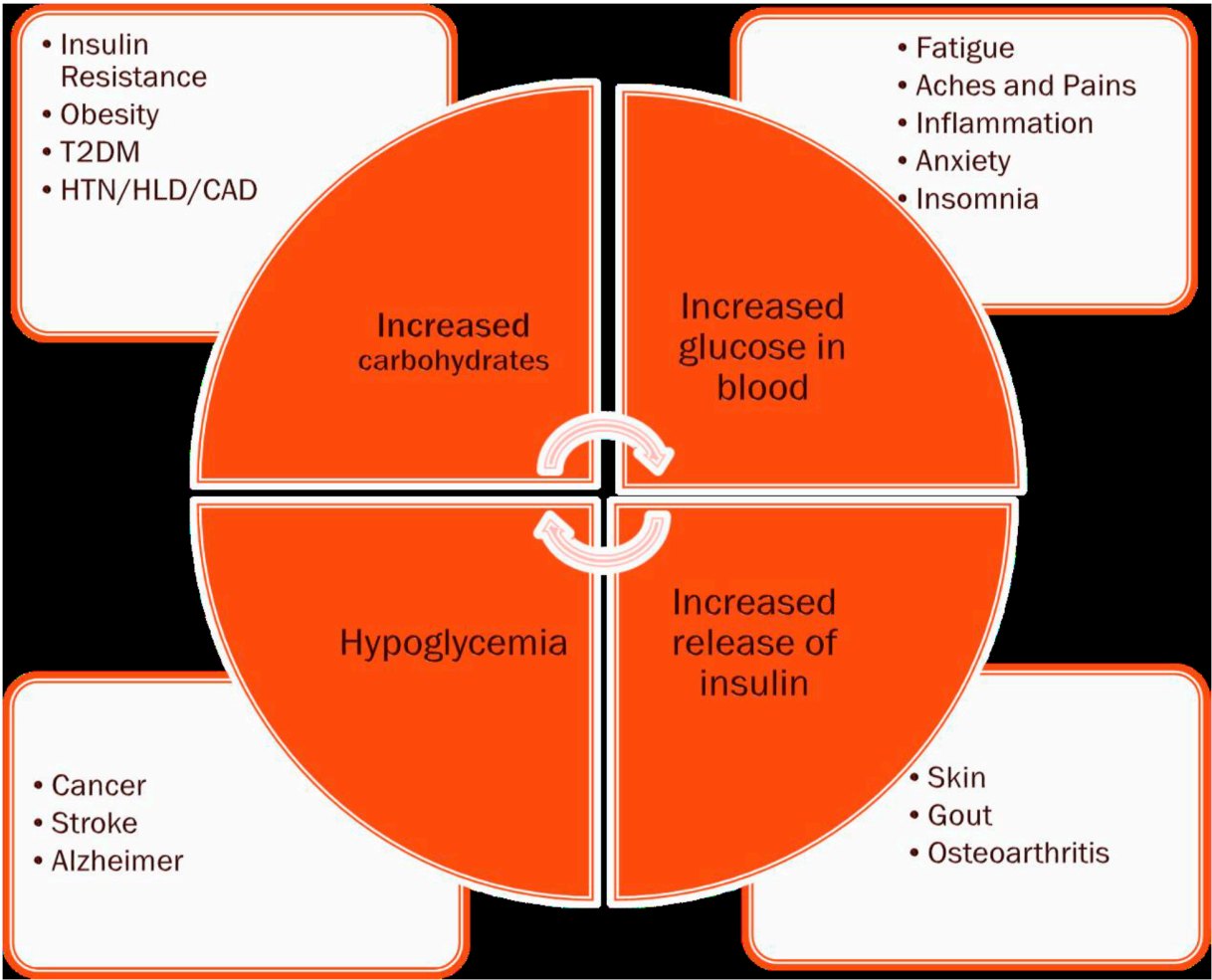
387   physically (fig. 3)

Figure 3. Insulin resistance Syndrome Cycle.

The available data reviewed in this paper points to several different approaches in the

nutritional management of IRS. A large and recent literature recommends a rational approach on

the macronutrient selection approach of removing saturated fats, restricting refined

carbohydrates and limiting animal protein. Dietary patterns have been extensively studied as

shown by the DASH, Healthy Eating Index, POUNDS LOST and Predimed studies. These

inform us of the importance of dietary compliance with the largest metabolic benefit coming

from moderate calorie intake and subsequent weight loss. People with IRS will benefit the most

397   by combining weight loss and anti-inflammatory nutrients (vitamins, flavonoids, and

398   unsaturated fatty acids) (Steckhan et al., 2016).

399   The addition of specific foods or micronutrients may be beneficial. There is high level

400   evidence to include monounsaturated fatty acids, probiotics (including yogurt), probiotics and

401   synbiotics, avocado, magnesium, vitamin D, green tea and resveratrol unless contraindicated.

402   The newly recommendation of precision/personalized medicine, taking in account the

403   genes, environment and lifestyle, should be applied in the case of patients with IRS. While

404   structure and accountability as well a good understanding of the condition has helped everyone,

405   when it comes to treatment, the approach should be individualized based on what we know such

406   a metabolism, microbiome, genetic makeup as well considering race, sex and environment. Each

407   patient should be recommended dietary approaches based on a comprehensive assessment and

408   diagnostic metabolic labs. One of the newly recommended biomarkers to be considered and

409   warranted for success will be the microbiome analysis. While there is much more we don't

410   understand yet, combating the global obesity with the knowledge and means we have will lead to

411   preventing IRS, sensitizing insulin on the people who have IRS and lead to better outcomes and

412   healthier lifestyles.

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