Cigarette Smoking: An Accessory to the Development of Insulin Resistance

Abstract: *Insulin resistance is a condition characterized by decreased sensitivity of a skeletal or adipose cell to insulin, resulting in decreased glucose uptake by the cell. This can lead to hyperinsulinemia and further reduce insulin sensitivity. Insulin resistance is one of the primary factors contributing to metabolic syndrome (MetS), causing elevated glucose and fatty acid concentrations in the blood. Smoking is associated with insulin resistance in a dose-dependent manner. It directly increases the risk for insulin resistance, mainly via hormone activation, and may indirectly cause insulin resistance due to its effects on abdominal obesity. Nicotine may be the factor underlying these potential mechanisms. With the prevalence of prediabetes and diabetes on the rise, and considering the role of smoking and its relationship to insulin resistance, smoking reduction or cessation may be a viable option for those who are at risk or already identified as insulin resistant. Therefore, smoking cessation or reduction would serve as a beneficial component in any diabetes prevention or treatment plan.*

Keywords: tobacco; cigarette smoking; insulin resistance; metabolic syndrome

Consumption of foods containing simple carbohydrates results in an increased concentration of glucose in the blood. This elevated blood glucose then stimulates the secretion of insulin from the beta cells of the pancreas. Insulin acts to aid the delivery of glucose into cells, particularly skeletal muscle and adipose tissue, which reduces the concentration of glucose in the blood. This action is brought about by an integral protein, known as GLUT4, that facilitates glucose transport into the cell.¹

Insulin resistance occurs when a cell has a reduced sensitivity to the concentration of insulin that it is exposed to. It results in inadequate control of blood glucose levels by normal insulin secretion and can result in increased insulin blood concentrations, known as hyperinsulinemia, to achieve the desired response.⁴ This compensatory hyperinsulinemia will further activate negative feedback mechanisms causing a downregulation of insulin receptors, decreased affinity of the receptors for

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Under normal metabolic circumstances, the binding of insulin to the insulin receptor on the cell membrane results in the recruitment of glucose transport proteins, mainly GLUT1 and GLUT4 to the cell surface, which facilitates the movement of glucose into the cell.² If insulin secretion or receptor activation is impaired, the translocation of GLUT4 is inhibited, and the cell is unable to take up glucose from the blood, resulting in insulin resistance.³

insulin, and a reduction in the insulin receptor's kinase activity,⁵ thus promoting even greater resistance to insulin.

Metabolic Syndrome

Insulin resistance is at the core of metabolic syndrome (MetS). The International Diabetes Foundation defines a person with MetS as one who has central obesity and 2 of the

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following 4 factors: elevated triglycerides (≥ 150 mg/dL), reduced high-density lipoprotein cholesterol (< 40 mg/dL in males; < 50 mg/dL in females), elevated blood pressure ($\geq 130/85$ mm Hg), and elevated fasting blood glucose (≥ 100 mg/dL).⁶ Insulin resistance not only results in elevated blood glucose, but it can also affect fatty acid concentrations in the blood. This relationship can be explained by the additional actions of insulin on blood lipids. Insulin resistance not only reduces glucose uptake by skeletal muscle cells, but it may also reduce the uptake of amino acids and fatty acids in the liver. This, in turn, reduces storage of glycogen and triglycerides.⁷ There is also a reduced uptake of circulating lipids and an increased hydrolysis of triglycerides in adipocytes, which contributes to an elevation of free fatty acids in the blood.⁸ The reduced glycogen synthesis and storage that occurs in the liver cells causes increased glucose production and release into the blood. These combined effects increase the level of blood glucose, instigating increases in insulin concentration levels in an attempt to mediate elevated blood glucose. If MetS persists and compensatory insulin secretion is ineffective, fasting blood glucose concentrations continue to increase and eventually develop into full type 2 diabetes.⁹

Smoking and Insulin Resistance

One lifestyle factor that may have direct and indirect effects on insulin resistance is cigarette smoking. Serum insulin concentrations have been shown to be greater in smokers compared with nonsmokers, even when controlling for factors that affect insulin resistance.^{10,11} Eliasson et al¹² found a dose-response relationship between quantity of cigarettes smoked per day and degree of insulin resistance. Furthermore, an acute impairment in glucose tolerance and increased insulin resistance was observed in both nonsmokers and smokers following the consumption of 3 cigarettes.¹⁰ In addition, insulin sensitivity

is improved with smoking cessation, despite increases in body weight that may occur.¹³ This suggests the potential for an independent direct effect of smoking on insulin resistance. Furthermore, smoking may have compounding effects as clinical evidence suggests that smoking is associated not only with insulin resistance but also with other factors that contribute to insulin resistance. For example, insulin resistance is often associated with visceral abdominal adiposity.¹⁴ An indirect linkage between insulin resistance and smoking arises from evidence suggesting that smoking is a contributor to visceral adiposity with the quantity of smoking associated with the degree of central obesity.¹⁵ In addition, adiponectin, a protein produced by the adipocytes that increases insulin sensitivity by enhancing blood glucose and fatty acid metabolism,¹⁶ may also be affected by cigarette smoking. Smoking is negatively associated with adiponectin levels and a dose-response relationship has also been reported.¹⁷ Furthermore, adiponectin levels have been found to increase following smoking cessation,¹⁸ suggesting that smoking may also affect insulin resistance through its action on adiponectin.

If there is an independent direct influence of smoking on insulin resistance, what is the underlying mechanism? It has been postulated that smoking may promote secretion of hormones such as cortisol, catecholamines, and growth hormone that oppose the effects of insulin. These hormones may cause an increase in lipolysis, promoting elevated levels of free fatty acids.^{19,20} Other potential contributors also have been identified, including a lessening of lipoprotein lipase (LPL) activity and decreased glycolytic enzyme activity.²¹ Since LPL hydrolyzes triglycerides into chylomicrons and very low density lipoproteins (VLDL) to stimulate the uptake of fatty acids by skeletal muscle and adipose tissue for energy storage,²² lower LPL activity, as observed in smokers,²³ may contribute to higher triglyceride concentrations in the blood.

High triglycerides in the blood may alter glucose metabolism by competing with carbohydrates for substrate oxidation where increased acetyl CoA (coenzyme A) and NADH (nicotinamide adenine dinucleotide) in the mitochondria from fatty acid oxidation would inhibit glycolytic enzymes, including pyruvate dehydrogenase, phosphofructokinase, and hexokinase II activity to create more glucose in the cell, thus inhibiting glucose uptake.²⁴ In addition, fatty acid metabolites can reduce the activity of insulin receptors by inhibiting their ability to activate PI (phosphoinositide) 3-kinase, an essential step of the insulin signaling pathway.²⁴

Furthermore, nicotine may be a mediating factor of this independent direct effect of smoking on insulin resistance.²⁵ Eliasson et al²⁶ found that long-term use of nicotine gum in the absence of cigarette smoke is associated with both insulin resistance and hyperinsulinemia. Additionally, increased lipolysis in adipose tissue due to nicotine-stimulated release of catecholamines has been reported.²⁷ Nicotine exposure may also increase levels of leptin, a hormone released by adipocytes that regulates food intake, which may be associated with insulin resistance.²⁸

Nicotine may serve a unique role in contributing not only to the direct effect of smoking on insulin resistance but also to the indirect impact by influencing body composition, in general, and visceral abdominal obesity specifically. While the mechanism underlying this relationship is not fully understood, nicotine can influence caloric consumption and energy expenditure by promoting the release of norepinephrine, serotonin, and other factors that can influence the brain to alter appetite and/or metabolic rate.²⁷ Initially, there could be a reduction in appetite and increased metabolic rate, but over time the chronic impact would increase appetite and decrease metabolic rate which contribute to increased body fat.²⁷ Elevated sympathetic nerve activity has also been associated specifically with abdominal adiposity²⁹ while nicotine may directly affect body fat through activation of

nicotinic cholinergic receptors on the adipose tissue.^{30,31} Nicotine also activates the hypothalamic-pituitary-adrenal axis, contributing to excess cortisol, a contributor to visceral adiposity.²⁰

If nicotine exerts dual effects, direct and indirect, on insulin resistance, research suggesting that nicotine delivery via cigarette smoking is dose dependent has important implications in attenuating the negative impact on insulin resistance.³² Furthermore, use of electronic cigarettes poses an additional concern as these alternatives also contain nicotine. While it has been observed that the amount of nicotine inhaled from an electronic cigarette is less than that of a traditional cigarette, more research is needed to determine the amount of nicotine that is delivered to the body and absorbed into the bloodstream from electronic cigarettes.³³

Implications for Public Health

At present, it is estimated that 86 million Americans (37%) are prediabetic, a condition that occurs as a result of insulin resistance, and is a component of MetS.³⁴ If unchecked, MetS is likely to lead to type 2 diabetes, an extreme form of insulin resistance. Attention to this public health menace has been focused primarily on obesity as the major contributor, and specifically visceral abdominal obesity, with less emphasis on other possible contributing factors, like cigarette smoking. If smoking is an important factor, it adds another layer of evidence supporting the need for smoking cessation in the population.

There is also evidence supporting a dose-dependent relationship between insulin resistance and cigarette smoking,^{32,35} with an 18% increased risk for developing diabetes with every 10 pack-year increase in cigarette smoking.³⁶ While more research is needed on the specific relationship between smoking reduction and insulin resistance, there is evidence supporting an improvement in risk factors for cardiovascular disease risk factors, stroke, and lung cancer with the reduction in the number of cigarettes

smoked.³⁷ In addition, those who reduce the number of cigarettes smoked are more likely to make an effort to quit smoking and succeed than those who quit without initially achieving smoking reduction.³⁸ Therefore, much could be accomplished by reducing the number of cigarettes consumed per day. This is an important message as smokers too often are given only one “either-or” choice, and that is to quit smoking entirely, or face dangerous health consequences. A reduction in the number of cigarettes smoked per day may be an embraceable middle ground for many smokers who are not yet ready to quit to improve not only insulin resistance but also other health outcomes related to smoking, including cardiovascular disease and cancer.

In conclusion, smoking has a direct and indirect influence on insulin resistance, a key factor in both metabolic syndrome and the development of diabetes. This relationship is most likely mediated by nicotine, a key ingredient in both cigarettes and electronic cigarettes, which are used by 15.1%³⁹ and 3.7%⁴⁰ of adults, respectively. With the prevalence of prediabetes and diabetes on the rise, smoking reduction or cessation may be a viable option for those who are at risk or already identified as insulin resistant. Therefore, smoking cessation or reduction would serve as a beneficial component in any diabetes prevention or treatment plan.

Declaration of Conflicting Interests

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