## Hyperinsulinemia and Insulin Resistance: Scope of the Problem



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### Introduction

At the beginning of the 20th century, infectious agents were the major causes of disease. The top three causes of death were pneumonia, tuberculosis and gastrointestinal infections. As a result of improved public sanitation and breakthrough developments in antimicrobial agents, these once formidable illnesses are now more rare and easily treated. In the 21st century, acute infectious diseases have been replaced by cardiovascular disease (CVD), cancer and diabetic complications as the most common causes of death.

The explosion of knowledge in genetics led to the discovery of many diseases that resulted from single genetic mutations. However, many modern, non-infectious chronic illnesses – the so-called 'diseases of civilisation' – do not fit the 'one gene, one disease' paradigm. Genetics obviously plays a role in susceptibility to disease, but just as obviously, the meteoric rise of these modern diseases cannot be the result of genetics alone.

Rather than 'unlucky genes', these conditions result from metabolic processes and cellular physiology derailed by poor diet, disrupted circadian rhythms, poor stress management, inadequate physical activity and other parameters by which modern lifestyles may be misaligned with the dietary and environmental landscapes humans are physiologically adapted to.<sup>1,2,3</sup> Among these conditions are ailments as diverse as type 2 diabetes (T2D), CVD,<sup>4</sup> Alzheimer's disease (AD),<sup>5,6,7</sup> acne,<sup>8,9</sup> gout,<sup>10,11,12</sup> erectile dysfunction,<sup>13</sup> polycystic ovarian syndrome (PCOS)<sup>14</sup> and conditions that are typically deemed 'idiopathic', such as vertigo and tinnitus.<sup>15,16,17</sup> A growing body of evidence suggests that these wide-ranging and seemingly unconnected conditions can, in fact, be linked to a common underlying cause: metabolic derangement resulting primarily from chronic hyperinsulinemia, and its eventual end point, insulin resistance (IR).

Virtually no medical specialty is unaffected by IR. From cardiology to endocrinology, paediatrics, gynaecology, ophthalmology, neurology and more, healthcare practitioners, treating patients from the cradle to the grave, regularly encounter pathological states that result directly from or are exacerbated by IR. However, currently there exists no forum to synthesise and unite the clinical findings and academic research across these diverse specialties. *The Journal of Insulin Resistance* is the vehicle through which this may be accomplished going forward.

The economic costs associated with IR are staggering. Diabetes-related expenditures totalled \$245 billion in 2012, with an increase to \$322 billion when factoring in undiagnosed diabetes, prediabetes and gestational diabetes.<sup>18,19</sup> Costs associated with AD alone are projected to exceed a *trillion* dollars by 2050, and projections for other illnesses are no less grim.<sup>20</sup> The exploding incidences of these conditions – which strike people ever younger – are a matter of national security, and financial security for individual families. Public health authorities, clinicians and patients alike can no longer afford to remain ignorant of the undeniable connections between IR and the wide range of pathological conditions currently causing such extensive morbidity and mortality. A large and continually expanding body of evidence suggests that IR is the cornerstone of a unifying theory of chronic disease.<sup>21</sup>

Hyperinsulinemia and IR are primary underlying factors either causing or exacerbating the illnesses that will bankrupt entire nations. A new treatment paradigm – which is quite different from the one currently employed – is urgently needed.

## The scope of the problem

The problems of hyperinsulinemia and IR are far greater than what is currently recognised in both the medical literature and clinical practice. While IR is rarely discussed outside the context of T2D,

millions of pre-diabetics and even non-diabetics remain at high risk. This reflects the limitations of a formal diagnosis of T2D based solely on abnormal blood glucose measurements. These include elevated fasting blood glucose (FBG), elevated haemoglobin A1c (HbA1c) and an abnormal response to an oral glucose tolerance test (OGTT).<sup>22</sup> The narrow focus on blood glucose dynamics ignores the larger and more insidious factor in the development of T2D and other epidemic diseases of the modern world: chronically elevated insulin.

Dr J. Kraft and colleagues discovered a staggering number of individuals with impaired insulin sensitivity missed by the traditional 2-h OGTT. Extending the OGTT to 5 h and including an insulin assay demonstrated that few individuals had truly healthy blood glucose and insulin responses.<sup>23</sup> The vast majority exhibited these 'normal' markers only as a result of dramatically elevated insulin.<sup>23,24</sup> Pathologically high insulin levels were keeping blood glucose within normal limits, leaving physicians with a false sense of safety regarding the true metabolic health of these patients.

Hyperinsulinemia or IR, rather than hyperglycaemia, may play the largest causal role in the pathology and progression of the modern chronic diseases. Elevated FBG and HbA1c are *late* indicators of metabolic dysregulation. It may be that the pancreas maintains its ability to secrete inordinate amounts of insulin, and muscle and adipose tissue remain sensitive to those elevated amounts for years, possibly decades, before breakdowns in physiology occur and the manifestation of hyperglycaemia becomes evident.

Therefore, normoglycaemic individuals are still at significant risk for the myriad conditions related to IR and resulting metabolic derangement. Family physicians are typically a patient's first point of contact with the medical system, and therefore may be in a position to identify insulin dysregulation in its earliest phases. However, direct measurement of fasting or post-prandial insulin levels is not currently a standard practice among these clinicians. In the absence of insulin testing, other parameters strongly suggest the presence of IR. These signs and symptoms overlap with those of metabolic syndrome (MetSy), which is regarded as a condition of IR and carbohydrate intolerance.<sup>25,26,27</sup> They include the following: decreased high-density lipoprotein cholesterol (HDL-C), large waist circumference, hypertension, elevated triglycerides and elevated FBG.28 Other markers that may add to the clinical picture include elevated homeostatic model assessment of insulin resistance (HOMA-IR),29 low-density lipoprotein (LDL) particles skewed towards small, dense 'pattern B',<sup>30</sup> elevated C-reactive protein<sup>31</sup> and elevated liver enzymes.<sup>32</sup>

Although obesity, as measured by body mass index (BMI), is one of the biggest risk factors associated with development of MetSy, patients with a 'healthy' BMI are not immune to the effects of insulin dysregulation. BMI is a useful metric in the epidemiologic assessment of entire populations, but it is far less accurate an indicator of the metabolic status of individuals. Heavier individuals with physiological markers that fall well within normal ranges are classified as the 'metabolically healthy obese',<sup>33</sup> while the converse of this – individuals with a healthy BMI, but several markers that place them squarely in a diagnosis of MetSy – are referred to as the 'normal weight obese'.<sup>34,35</sup>

Body weight is an unreliable indicator of current health and future disease risk, as normal-weight metabolic syndrome patients are at greater risk for morbidity and mortality than overweight individuals free of metabolic derangement.<sup>36,37</sup> For too long, overweight and obesity have been considered primary drivers of diabetes, heart disease, inflammatory disorders, etc., despite the fact that there are millions of normal-weight individuals who experience these conditions.

The accumulation of excess adipose tissue may be the result, rather than the cause, of the same underlying insulin dysregulation central to the development of the metabolic syndrome. This may help explain why some individuals develop obesity while others do not, because obesity may be only one manifestation of IR, albeit the most outwardly obvious. People may exhibit other manifestations of IR even in the absence of excess adiposity. Increased abdominal circumference and a large waist-to-height ratio are indirect indicators of IR.<sup>38</sup>

Moving beyond BMI and anthropometric measurements, even across the entire spectrum of body weight, chronically elevated insulin is associated with – and may be a primary driver of – the dominant health scourges of our time: CVD, cancer and AD. These pathologies may be present even in the absence of chronic hyperglycaemia, although the combination of IR with hyperglycaemia greatly compounds the effects.

The extent to which CVD is a manifestation of IR is greatly underappreciated. In a Japanese cohort of non-diabetic individuals aged 46–80 years old free of CVD (n = 29059), followed for a median of 9.4 years, 935 CVD events were recorded (770 strokes and 165 coronary heart disease). After adjustment, a non-linear association was observed between HbA1c levels and CVD risk. Compared with HbA1c levels of 5.0% – 5.4%, the hazard ratio (HR) for CVD was 1.77 (95% CI: 1.32-2.38) for HbA1c levels 3 6.5%.39 These findings echo those of other studies. Elevated HbA1c within the nondiabetic range is an independent risk factor for CVD - in particular, ischemic stroke and coronary heart disease.<sup>40</sup> With emphasis again on non-diabetics, the continuous and significant association between elevated A1c persists independent of age, BMI, waist-to-hip ratio, systolic blood pressure, serum cholesterol and smoking. In a British cohort (n = 10232, 4662 men and 5570 women), excluding individuals with a history of CVD or HbA1c > 7.0%, diagnosed diabetics accounted for 15.0% of the deaths in the sample, compared to 72.0% occurring in individuals with HbA1c between 5.0% and 6.9%.41 With elevated HbA1c not prompting a formal diabetes diagnosis until it exceeds 6.5%,42 it's clear that increased risk for CVD may be missed for millions of people with HbA1c within the normal or pre-diabetic ranges, and who would otherwise be classified as 'apparently healthy'.43

Cancer, too, has undeniable associations with IR. Cancer cells, regardless of tissue type, are characterised by aberrant

glycolytic metabolism. Cancer cells have mitochondria that are reduced in number, function or both. Thus, they are unable to generate ATP efficiently via oxidative phosphorylation and instead revert to rampant glycolysis and a more primitive form of energy generation: 'aerobic fermentation' – fermentation even in the presence of oxygen, known as the Warburg effect.<sup>44,45,46,47</sup> With significant impairment in cancer cells' capacity to oxidise fatty acids and ketones, IR and chronic hyperglycaemia provide cancer cells with a large and continuous supply of the fuel substrate they metabolise most effectively: glucose.<sup>48</sup>

In addition, chronic hyperinsulinemia may promote carcinogenesis via stimulation of insulin-like growth factor 1 (IGF-1), modulation of sex hormones and through promotion of inflammation.<sup>49</sup> Beyond an increased incidence of cancer, IR and elevated HbA1c are also correlated with worse prognosis in patients undergoing active treatment.<sup>49,50</sup> Even within the normal range, HbA1c is positively correlated to an increased risk for all cancers (excluding that of the liver), which mirrors the increased risk for CVD.<sup>51</sup> Metabolic syndrome, IR and hyperglycaemia are all associated with breast cancer recurrence, which has many oncologists and dietitians calling current dietary guidelines into question.<sup>52</sup>

AD is now frequently referred to as 'diabetes of the brain' or 'type 3 diabetes', bringing immediate attention to the role of insulin dysregulation and impaired blood glucose.<sup>53,54</sup> A wealth of research implicates brain IR in the pathology and progression of this condition.<sup>55,56</sup> Indeed, elevated HbA1c is a strong risk factor for greater progression of brain atrophy among the elderly.<sup>57</sup> Even among non-diabetics, the risk for future cognitive decline is positively associated with higher fasting insulin levels and HOMA-IR at baseline.<sup>58</sup> Among a cohort of individuals aged 65 or older without dementia, the risk for developing AD was double among non-diabetics with fasting hyperinsulinemia compared to those with normal fasting insulin levels.<sup>59</sup> These are individuals whose increased risk for cognitive impairment and AD would be missed by standard blood testing looking only at fasting glucose and A1c.

## The effect of insulin on multiple body systems

There are multiple mechanisms through which the pathophysiological cascade initiated by IR may be responsible for the development of such seemingly disparate conditions as T2D, CVD, AD and male and female reproductive abnormalities.

Hyperglycaemia leads to pathologic protein glycation, which may compromise the function of multiple organs and tissue systems, including the eyes, kidneys, blood vessels, peripheral nerves and the blood itself.<sup>60,61,62</sup> This is most clearly demonstrated by HbA1c and fructosamine measurements.

As an anabolic hormone, insulin plays a key role in fuel partitioning and metabolism. Abnormalities of insulin regulation may lead to an overloading of fuel substrates into the mitochondria. The resulting oxidative stress leads to eventual mitochondrial dysfunction or destruction, which has been implicated in the pathology or progression of conditions not typically associated with IR, such as multiple sclerosis,<sup>63,64,65</sup> AD,<sup>66,67</sup> Parkinson's disease<sup>68,69</sup> and cancer.<sup>44,70</sup>

Chronic hyperinsulinemia may promote systemic inflammation,<sup>71</sup> in part by influencing desaturase enzymes involved in the inflammatory process (via catalysing the conversion of omega-6 linoleic acid into inflammatory prostaglandins and other signalling molecules).<sup>72</sup> Chronic, unresolved inflammation and oxidative stress are increasingly recognised as underlying factors in atherosclerosis and other forms of heart disease.<sup>4,73</sup>

Insulin profoundly influences sodium and fluid dynamics, and therefore may play a role in idiopathic hypertension even in the absence of other signs of MetSy. Hyperinsulinemia, compounded with hyperglycaemic glycation of the fragile renal tubules, results in overall fluid retention, manifesting as oedema.<sup>10,74</sup>

Insulin influences sex hormone dynamics in both men and women by upregulating expression of the aromatase enzyme, responsible for converting testosterone into oestrogen. This may partially underlie the increasing incidence of gynaecomastia, prostatic hypertrophy or hyperplasia, decreased libido and general sexual dysfunction in men.<sup>75</sup> In women, PCOS has long been recognised as a hyperinsulinemic condition that frequently manifests along with increased androgens, resulting in hirsutism and other signs of masculinisation, as well as menstrual abnormalities and infertility.<sup>76,77,78</sup>

# Pathophysiology of insulin resistance

Several theories have been put forward regarding the development of IR. There is likely not a single cause, rather a confluence of factors that exert their influence over time and eventually result in metabolic dysregulation. These include, but are not limited to, the following:

- excessively high refined carbohydrates in the diet, resulting in a glycaemic load that overwhelms human physiological regulatory mechanisms<sup>79,80</sup>
- biologically inappropriate amounts of polyunsaturated fatty acids (specifically, omega-6 linoleic acid, coming primarily from isolated vegetable and seed oils, such as soy, corn and cottonseed)<sup>73,81</sup>
- insufficient dietary omega-3 fatty acids, particularly when coupled with excessive intake of omega-6 fatty acids<sup>82,83,84,85,86,87</sup>
- disrupted circadian rhythms and an extended photoperiod, which may have an adverse influence on internal biorhythms and the pulsatile secretion of hormones, including cortisol and human growth hormone<sup>88,89,90,91</sup>
- reduced physical activity, affecting mitochondrial biogenesis, skeletal muscle glucose uptake and insulin sensitivity<sup>92,93,94,95,96</sup>

 increased feeding opportunities – decreased time between meals, allowing less time for a return to baseline in hormones that regulate blood glucose, appetite and fuel partitioning, such as insulin, glucagon and leptin, and reduced time for autophagy and cellular repair.<sup>97,98,99</sup>

This is but a small selection of the host of factors purported to contribute to the development of IR. There may be many more. *The Journal of Insulin Resistance* will be a forum for highlighting new findings related to these and yet-to-emerge theories regarding the aetiology, treatment and prevention of IR.

#### A new paradigm

Modern medicine remains mired in a myopic and outdated paradigm of searching for a single pathogenic cause for each separate illness encountered – a one-to-one match, like a key fitting into a lock. Researchers and clinicians continuously look for 'silver bullet' cures for the various modern diseases. This approach worked well for infectious diseases caused by pathogenic organisms, but it is clearly failing to have an impact on the current epidemic of metabolic diseases, which are not infectious in origin.

Instead, understanding that many modern diseases are dietary and environmental in nature leads us to the inescapable and logical conclusion that the solutions are to be found in dietary and lifestyle interventions.

Virtually, no body system is unaffected by chronic hyperinsulinemia, IR and the accompanying hyperglycaemia. Therefore, the time has come for a new paradigm, recognising the primacy of insulin dysregulation as a unifying factor of chronic disease. As the various diseases associated with the MetSy may be relatively *late* indicators of IR that manifest only after the body's compensatory mechanisms have begun to fail, then early identification may be one of the most powerful and profound tools for modern medicine in stemming the destructive tide of these illnesses.

By addressing hyperinsulinemia and IR, it is possible to treat the root cause, rather than the symptoms, of these myriad diverse conditions. Symptomatic treatment alone leads to disease progression, necessitating ever higher doses and new forms of medication, as well as expensive surgical procedures. By potentially obviating the need for pharmaceutical drugs that are ineffectual at influencing the underlying cause(s) of these illnesses, this new paradigm may reduce the inherent dangers of polypharmacy and the incidence of undesirable and often harmful side effects of medication prescribed to ameliorate the effects of other medication.

Indeed, patients are typically told their chronic illnesses are progressive and irreversible. It may be, however, that this prognosis is accurate only insofar as it reflects the current symptom-oriented treatment paradigm. Alternatively, if treatment is reoriented towards correcting the primary underlying metabolic disturbances, then patients may be motivated to take a more proactive role in their own care and it may well be possible to reverse these so-called 'diseases of civilisation'.

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