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REVIEW

Hyperinsulinemia: Best management practice

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ABSTRACT

Chronic hyperinsulinemia associated with insulin resistance is directly and indirectly associated with many metabolic disorders that contribute to significant morbidity and mortality. Because hyperinsulinemia is not widely recognised as an independent health risk, there are few studies that assess management strategies. Medication management may not address the multiple issues associated with hyperinsulinemia. Lifestyle management includes physical activity, especially high intensity interval training, and dietary management. Reducing carbohydrate quantity and increasing nutrient density are discussed with carbohydrate-restricted and Mediterranean diets conferring additional benefits to a low-fat diet. Physical activity and dietary management provide the foundation for hyperinsulinemia management and may work synergistically. Of these principles, a combination of resistance and high intensity interval training, and carbohydrate restriction provide the two most effective frontline management strategies for managing hyperinsulinemia.

Keywords: *Hyperinsulinemia, hyperglycemia, type 2 diabetes, insulin resistance, secretagogue, syndrome x*

Introduction

Compensatory hyperinsulinemia (further referred to as "hyperinsulinemia") is associated, mechanistically and epidemiologically, with many chronic metabolic diseases.[1, 2] The aetiology of hyperinsulinemia is likely heterogeneous[2] and in the earliest stages asymptomatic.[3] Early management of hyperinsulinemia may prevent, delay, or mitigate the severity of subsequent pathologies. Although hyperinsulinemia is a common co-pathology with impaired glycemic control, this paper focuses on the management of hyperinsulinemia in the presence of normal glucose tolerance.

There are several different states that depict the continuum that reflects healthy insulin response through to hyperinsulinemia. It is proposed that people transition between different states, which may be either acute or chronic, depending on the circumstances at the time, and may be subject to change. The close relationship between the two different states of hyperinsulinemia and insulin resistance can also be noted. This means that as well as targeting insulin levels directly, strategies that improve insulin sensitivity, especially the up-regulation of glucose transporter type 4 (GLUT4), will also reduce hyperinsulinemia. As there are few studies that directly assess hyperinsulinemia management strategies, this review will include strategies that improve glycemic control in the absence of evidence of increased insulin secretion. It will also consider strategies that provide symptomatic improvement of conditions associated with hyperinsulinemia such as polycystic ovarian syndrome (PCOS).

There are two main strategies for managing hyperinsulinemia: maximising insulin sensitivity and reducing glycemic load. Insulin sensitivity can be maximised via up-regulating GLUT4 or insulin receptors, or by preventing (further) insulin resistance. Glycemic load may occur through two main pathways, endogenous through metabolic pathways such as gluconeogenesis, glycolysis, or renal reabsorption[4], and exogenous via dietary intake.

There are three main mechanisms to achieve each of these strategies: Physical activity, diet, and medicines and other supplements.

Methodology

Literature was reviewed on hyperinsulinemia and insulin resistance, targeting full-text English language studies. There was no date criterion. Articles were selected on the basis of having a minimum of both a plausible biological mechanism and established clinical association. An academic database search included EBSCO, Medline and Google Scholar, using variants of the terms "hyperinsulinemia," "insulin resistance," "type 2 diabetes," and "metabolic syndrome," and each of these terms in conjunction with variants of "diet," "nutrition," "physical activity," "pharmacology," and "treatment." References were based on the authors' judgment of relevance,

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completeness, and compatibility with clinical, epidemiological, pathological and biochemical criteria.

Physical activity

Physical activity is well-documented for improving insulin sensitivity. Mechanistically this occurs via GLUT4 up-regulation, increased hexokinase gene transcription[5], increased fuel consumption and, if sustained, decreases to insulin secretion.[6] Conversely, sustained physical activity can also increase glucagon, cortisol and catecholamine secretion.[6] These hormones can all increase gluconeogenesis and if unbalanced, impair rather than improve insulin sensitivity. Very intense physical activity stimulates insulin production, especially in the presence of hyperglycemia. Without question, physical activity will be a key component for managing hyperinsulinemia, but the question remains whether different forms of physical activity can maximize sensitivity while minimizing counter-hormones.

Physical activity can be broadly divided into two main classifications that have considerable overlap: resistance training and aerobic activity. The latter has a further subset: high intensity interval training (HIIT).

Resistance training

Resistance training is characterized by muscles contracting against an external resistance causing brief and isolated activity of single muscle groups.[7] The health-benefits of resistance training are well-recognized. These can include decreases to HbA1c, weight, body fat, and blood pressure.[8] Other improvements include increases to bone mineral density, and lean body mass. There are also potential benefits to mood and cognition, balance and falls-risk, and overall self-esteem.

Resistance training may improve hyperinsulinemia through three main mechanisms: increasing, or maintaining muscle mass, glucose expenditure and enhancing the cellular metabolic capacity. It is estimated that inactive adults lose 3-8% of muscle mass per decade accompanied by a reduction in resting metabolic rate[8] Losing muscle mass means that glucose disposal will be harder resulting in increased adiposity. Increased muscle mass is posited as one explanation for the improvements in glucose disposal rates for resistance training.[9] This is because both weight lifters and long-distance runners show increased glucose disposal rates compared to controls; however, this difference remains only for the long-distance runners after differences in lean-body-mass are taken into account. This is consistent with other studies comparing aerobic to resistance training, which only showed improvements in glucose disposal when the results were expressed per kilo of fat-free-mass.

While resistance training is believed to enhance cellular metabolic capacity by mechanisms such as GLUT4 mobilization[9], potentially negative effects by way of increased cortisol are also observed. Crucially, fewer repetitions and longer rest periods between sets elicit a lower cortisol response, which may be important for beginners to resistance training.[10] Increased catecholamine and/or insulin secretion may also be observed with resistance training. These changes may also be exercise-dose dependent and may attenuate as training adaptation occurs. An elevated insulin response is associated with protein/carbohydrate supplementation. Elevated hormonal responses may also be associated with overtraining.[10]

Aerobic exercise

Aerobic exercise can be broadly described as light to moderate intensity activities that can be performed for extended periods of time. Examples of aerobic exercise include walking, jogging and swimming. There is a large body of literature on the type and amount of aerobic activity required to maintain health. Conventional wisdom suggests that a minimum of 30 accumulated minutes of moderate intensity activity (ie. brisk walking) should occur on most days to achieve health benefits[11], although the efficacy of this volume has since been questioned.[12] Aerobic exercise is believed to improve metabolic health via the same mechanisms as resistance training.

A meta-analysis comparing resistance training to aerobic exercise concluded that clinically, there were no advantages between resistance training and aerobic exercise for lowering HbA1c or impacting cardiovascular risk.[7] However, aerobic exercise was modestly advantageous for lowering BMI. Resistance training may confer greater benefit to those with limited mobility as many of the exercises can be performed by the sedentary.

High intensity interval training (HIIT)

HIIT protocols are a subset of aerobic exercise characterized by short, maximal-intensity, anaerobic exercise sessions separated by medium or low intensity periods for recovery. There are several advantages to HIIT protocols compared to conventional aerobic exercise: time; glucose utilization and cellular metabolic capacity. Lack of time is the biggest reason cited for not exercising.[9] HIIT protocols allow for greater power output for an

equivalent amount of energy expenditure but in a shorter period of time[13] resulting in greater improvements to cardiorespiratory fitness.[14] Other benefits of HIIT compared to conventional aerobic training include greater reductions of skinfold thickness and decreased $AUCi_{nsulin}$.[15, 16] HIIT protocols may have further advantages over traditional aerobic exercise regimes as they can be used safely and effectively in people following cardiac stenting, coronary artery grafting and myocardial infarction. Musculoskeletal injuries were no more common than that found with other forms of exercise.[14, 17-19] These results demonstrate that HIIT is safe and effective when performed under controlled conditions. Patients new to HIIT may require specific assessment and/or instructions from an exercise physiologist or physiotherapist.

GLUT4 adaptation can occur with single bouts of exercise and effects persist for up to 40 hours.[20, 21] This suggests that, especially in the early days of adopting physical activity, varying the activities undertaken may maximize GLUT4 adaptation while minimizing effects from over-secretion of cortisol or glucagon. While the literature suggests the ideal activity should comprise a combination of resistance training and HITT protocols, the final selection of physical activities may be influenced by personal circumstances, including preference, health status and levels of training required.

Diet

There is considerable public and scientific debate and discussion concerning the optimal dietary approach for the management of metabolic dysregulation. Without discussing macronutrient proportions, it is generally agreed that a healthy diet should predominantly be comprised of the following: 1. whole foods[22], 2. adequate protein and other currently established essential nutrients including water, specific vitamins, minerals, electrolytes and fatty acids[23], 3. adequate energy, 4. aequate fiber, although fiber may not be considered aequate, there is sufficient evidence to support its inclusion.[24-26] A diet that limits the risk of, or manages the effects of, hyperinsulinemia should also consider the following: 5. prevents acute hyperglycemia, whether via either exogenous carbohydrate or gluconeogenesis, thus preventing acute hyperinsulinemia, 6. prevents caloric overload, thus limiting both the amount of energy to be stored as fat and the potential for hyperglycemia, 7. limits items known to down-regulate GLUT4 or insulin receptors (e.g. arachidonic acid), 8. promotes items known to up-regulate GLUT4 or insulin receptors and finally 9. causes sufficient satiety so that hormones, receptors and transporters are not over stimulated.

Adherence factors, including adverse reactions should also be considerations. Adherence is recognized as being key to weight-loss.[27] Traditionally, obesity is seen as the driver of many metabolic diseases, so weight-loss is the first step to improved health.[28] However, the metabolic theory of disease states that metabolic changes including hyperinsulinemia may precede weight gain. Under this model, weight-gain is the first visible symptom of metabolic disease, therefore weight-loss should also indicate health improvements. This means that dietary adherence will also be associated with improvements to hyperinsulinemia.

Dietary research is complicated as many studies use "standard" diets as the control. This "standard" diet is generally low in fruits and vegetables and high in sugars and refined carbohydrates.[29] As this diet will likely be lacking in essential nutrients and fiber, cause acute hyperglycemia, and have excessive calories, any dietary regime that reverses these trends will show improvements to health. Furthermore, diet-health research often employs weight loss as the primary end-point, rather than other metabolic markers, yet improvements to metabolic markers are possible without significant weight changes.[30] However, any dietary approach that causes weight loss, will improve hyperinsulinemia as body fat can only be stored, rather than oxidized in the presence of high insulin levels.[31] Therefore both improved glycemic control and weight loss can be used as proxies for improved hyperinsulinemia.

There are three distinct dietary approaches (low fat; Mediterranean; and carbohydrate-restricted) that are shown to improve glycemic control. Improved glycemic control may indicate improved insulin response, so these diets should be considered for managing hyperinsulinemia. Although there is some evidence to support high protein diets for the treatment of diabetes, excess protein will induce gluconeogenesis, thus breaching criterion 4. Therefore, only moderate protein diets will be considered in this review. As few studies directly target hyperinsulinemia, the question remains are any of these three approaches superior to the others for managing hyperinsulinemia?

Low-fat

Currently, the low fat, high carbohydrate dietary approach is considered to be standard practice for managing diabetes by many authorities. For adults (aged 19 and older) this regime generally comprises 20-35% fat, (< 10% saturated fats), 10-35% protein

and 45-65% carbohydrate.[32] Fruits, vegetables and whole-grains are recommended as carbohydrate and fiber sources, while vegetable oils (excluding coconut, palm and palm kernel oils) are emphasized as healthy fat sources.[29] Lean protein, including fat-free or low-fat dairy products, or vegetable protein sources, are also recommended.

Mediterranean

Although there are a variety of "Mediterranean" dietary approaches[33], the term generally defines a diet that comprises a high amount of monounsaturated fatty acids (MUFA), predominantly from olive oil (35%), fruits and vegetables, whole-grains and fish; moderate amounts of alcohol and small amounts of red meat, sugars and refined grains.[34, 35]

Carbohydrate-restriction

Like the Mediterranean diet, there is no clear definition of a carbohydrate-restricted diet. Daily carbohydrate intake has been defined as 12-40% of daily energy intake or < 20 -150g/day (36-39). To ensure adequate energy, the fat content of the diet is increased, up to about 75% of daily energy content.

Comparison of different dietary strategies

Each of these diets have notable benefits for the management of diabetes compared to standard diets.[40-42] It is traditionally considered that weight management is the key driver behind metabolic improvements, hence the previous favour of the low-fat (and consequently low-calorie) diet. However, emerging research suggests that increased benefits to metabolic health can be found from diets higher in fats and lower in carbohydrates. A meta-analysis compared Mediterranean diets to low-fat diets in overweight/obese people (n = 2650, 50% female) over two years of follow-up. Those following the Mediterranean diet had greater improvements to body weight and BMI, systolic and diastolic blood pressure, fasting glucose, total cholesterol, and high-sensitivity C-reactive protein (hs-CRP).[35] While some of the effects were modest, the weighted mean differences clearly favoured the Mediterranean diet. This suggests that low-fat diets may not be optimal for managing diabetes, or hyperinsulinemia.

Although this study does not directly assess hyperinsulinemia, the improvements to the other metabolic markers, especially fasting glucose, imply improvements to hyperinsulinemia. There are several potential mechanisms for these observations. Firstly, the lower carbohydrate content and therefore glycemic load means that acute hyperglycemia, and hence acute hyperinsulinemia is less likely.[43]. Fewer glucose molecules to be absorbed into the cells reduces metabolic stress. MUFA are believed to enhance insulin signaling[44] whereas using omega-6 rich polyunsaturated oils may lead to an increase in arachidonic acid, which may down regulate GLUT4.[45]

The Mediterranean diet is also associated with a high degree of satiety.[46] Satiety may help to prevent overeating and allow longer periods of fasting. Restricting carbohydrates have also been shown to confer additional health benefits compared to low-fat diets, especially with respect to weight, lipid profile, glycemic control, and potentially kidney function.[47-50] There are few large studies that compared the effects of carbohydrate restricted diets to the Mediterranean diet. However, restricting carbohydrates conferred greater weight loss, a larger decrease in triglycerides and hsCRP, and larger increase to HDL after six months of dietary intervention.[36] The Mediterranean diet favored a decrease in fasting glucose in people with diabetes. The differences between the two diets had narrowed by 24 months but both showed improvements compared to a low-fat diet.

A key hyperinsulinemia management strategy is to prevent hyperglycemia and insulin secretion. This may explain the additional benefits to carbohydrate restriction. There are concerns regarding carbohydrate restriction, predominantly concerning high dietary fat. High fat consumption, especially saturated fats, is traditionally associated with adverse metabolic outcomes. However, studies conducted over two years have not found additional health risks.[51] Furthermore, high-fat dairy has been found to decrease the incidence of type 2 diabetes and the risk of death or hospitalization due to coronary heart disease, compared to low-fat dairy.[52, 53] It is now believed that there are sub types of saturated fats which have different health effects.[54]

Hyperinsulinemia encompasses a range of severities. All three dietary strategies discussed above have the potential to improve the disorder. Logically, carbohydrate consumption in excess of what the body can tolerate, will invoke excessive insulin secretion. Therefore restricting carbohydrates to a tolerated level should confer maximal health benefit, especially if the person consumes a whole-food diet based on Mediterranean principles. However, effective dietary management may be governed by adherence to the chosen regime.[27, 55]

Isolated beneficial nutrients / foods

Other compounds that have been shown to improve glycemic control include magnesium, chromium, garlic, cinnamon, and green tea.

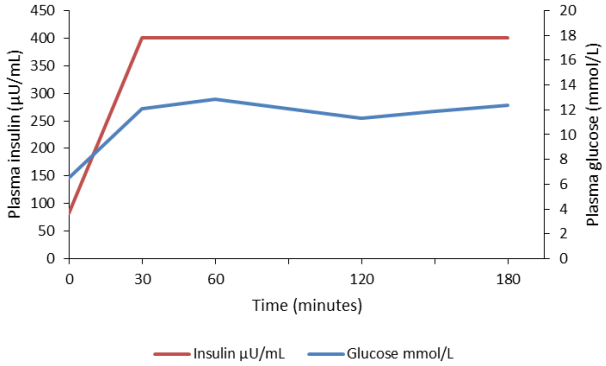

Figure 1: Glucose and insulin response curves following an oral glucose tolerance test in a patient with type 2 diabetes on insulin who inadvertently injected her normal morning insulin prior to the test. Data reproduced from Kraft[77]

Magnesium is believed to improve GLUT4 expression in rodent studies independently to insulin action.[56] Chromium may improve insulin receptor sensitivity.[57] There is some evidence to suggest many people are chromium deficient, especially if they eat highly refined foods, which, are not only unlikely to contain sufficient chromium, can also exacerbate its loss.[58] Emerging evidence suggests that magnesium and chromium may work synergistically to improve glycemic control.[59] Foods rich in these minerals are key components of the Mediterranean diet, especially nuts and whole grains. Green tea supplements, garlic and cinnamon[60-62] may also be beneficial improving insulin sensitivity, but the mechanisms are not fully elucidated.

There are a number of traditional remedies for treating type 2 diabetes that may be beneficial for managing hyperinsulinemia including (but not limited to) berberine[63, 64], fenugreek[65, 66], bilberries[67], and black cumin.[68, 69] While the mechanism of actions of these products are not fully elucidated, they are posited to include 5' adenosine monophosphate-activated protein kinase (AMPK), (berberine) similar to that of metformin[70] or preventing carbohydrate absorption (bilberries, fenugreek). It is necessary to further assess the effect of these remedies on insulin release as both berberine and black cumin are posited to increase insulin release, although reports are mixed.

Medications

As previously stated, this review is predominantly concerned with hyperinsulinemia in the presence of normal glucose tolerance. However, as people with impaired glycemic control, are likely to be hyperinsulinemic[3] plausibly, strategies that improve glycemic control without aggravating hyperinsulinemia may optimize health. Other medications that affect hyperinsulinemia may not be prescribed for metabolic disease; however, understanding this adverse effect is important.

There are two main medication strategies for managing hyperinsulinemia: eliminating those that aggravate insulin resistance or contribute directly to hyperinsulinemia; and prescribing medications that improve insulin sensitivity. The latter should be considered second-line to lifestyle management. Medication management will be limited especially if hyperglycemia, or other clinical conditions, need to be considered. For example, both antipsychotic medications, and longer courses of prednisone are known to aggravate insulin resistance and increase the risk of developing type 2 diabetes.[71] However, stopping these medications in many patients may be inappropriate so alternative strategies need to be considered.

Medications that theoretically worsen hyperinsulinemia

Medications may induce hyperinsulinemia by: GLUT4 down-regulation; hyperglycemia (via increased appetite, or affecting hormones such as adrenaline or cortisol); or directly increasing insulin secretion. These properties, especially GLUT4 down-regulation, may be difficult to discern from medication data sheets. If listed side-effects include weight gain or an increased risk of developing type 2 diabetes, then hyperinsulinemia should be a reasonable suspicion.

	Improved by	Worsened by	Indeterminate
Insulin receptor availability	Time Chromium MUFA	Hyperglycemia Hyperinsulinemia Cortisol Highly refined foods	
GLUT4 up regulation	Magnesium Metformin Physical activity Time	Excessive physical activity Arachidonic acid	
Hyperglycemia	Carbohydrate-restricted diets Mediterranean diet Physical activity Black cumin	Excessive physical activity Excessive protein Excessive carbohydrate	High-carbohydrate, Low fat diets
Hyperinsulinemia		Insulin Insulin secretagogues Insulin mimetics Very intense physical activity Excessive protein Excessive carbohydrate	Berberine Black cumin
AMPK activation	Berberine		
Reduced carbohydrate absorption	Carbohydrate-restricted diets Bilberries Fenugreek	Excessive dietary carbohydrate	
Mechanism unknown	Green tea Garlic Cinnamon		

Table 1: Summary of management strategies for managing hyperinsulinemia

Medications known to down regulate GLUT4 include: clozapine[72]; ritonavir[73]; statins[74]; and corticosteroids.[75]

Plasma insulin is increased by exogenous insulin, insulin secretagogues, or insulin mimetics, prescribed to manage hyperglycemia. Although the insulin secretagogues such as sulphonylureas are less commonly used.[76], little is known about the effects of these medications on hyperinsulinemia. An unpublished case report suggests exogenous insulin used in type 2 diabetes can produce insulin spikes > 400 μU/mL for a number of hours following a 100g glucose load[77] as shown in Figure 1. The maximal insulin concentration remains unknown as the reference standard was only calibrated to a maximum of 400 μU/mL.

Despite this degree of serum insulin elevation, it can be noted that the patient did not attain a normal glycemic profile. The combination of hyperglycemia

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and hyperinsulinemia increases the risk of a poor long-term prognosis for this patient. Further research is required to establish if this is an isolated situation or the standard response for many patients with type 2 diabetes.

Medications potentially beneficial for hyperinsulinemia

Although the somatostatin analogue, octreotide, is used to treat isolated hyperinsulinemia, (e.g. insulinoma)[78, 79], compensatory hyperinsulinemia cannot be managed without concurrent glycemic control. Hyperglycemia is well recognized to have adverse pathologies, including diabetic ketoacidosis. But ketoacidosis can be triggered by low insulin levels independent of glycemic status. Increasing levels of glucagon and cortisol may be triggered by cellular starvation, or hypoglycemia. These hormones can induce gluconeogenesis and glycogenolysis leading to overproduction of the ketone bodies acetoacetic acid, β-hydroxybutyrate and acetone.[80] Both acetoacetic acid and β-hydroxybutyrate are strong acids. Under normal circumstances insulin levels help to regulate the production of these ketone bodies, but in its absence potentially fatal ketoacidosis may develop.

Thiazolidinedione-type insulin sensitizers, such as rosiglitazone, improve peripheral glucose uptake without increasing serum insulin levels[81] However, all insulin sensitizers increase substrate uptake, which has implications for the formation of reactive oxidative species (ROS) and advanced glycation end-products (AGEs) and their adverse health effects.[82, 83] Furthermore, the use of thiazolidinediones is considered controversial because of their association with significant adverse effects such as heart failure, fracture risks, and increased risk of bladder cancer.[84, 85]

Metformin is the most promising (albeit limited) medication to manage hyperinsulinemia as it up-regulates GLUT4.[86] However, unlike the thiazolidinediones, metformin also inhibits gluconeogenesis in the liver and/or delays glucose absorption from the gastrointestinal tract.[87] These latter actions may better reduce overall glucose load and therefore decrease endogenous insulin secretion. However, emerging research suggests metformin may not be beneficial for treating type 2 diabetes.[88] Metformin may also cause excessive cellular nutrient uptake leading to increased ROS and AGEs.[83] Research does support the use of metformin for treating PCOS, a condition associated with hyperinsulinemia.[86] However, pharmacological management of hyperinsulinemia in the absence of another pathology cannot be supported by the current literature.

Novel mechanisms

Future targets for pharmacological management of hyperinsulinemia may include insulin degrading enzyme (IDE) and the forkhead transcription factor (FOXA-2). IDE mediates multiple hormones including insulin and glucagon. Rodent studies indicate impaired IDE, with resultant hyperinsulinemia associated with poorer glycemic control (89). However, further research in this field may be able to selectively target glucagon. FOXA-2 has been shown to improve insulin sensitivity in a number of mouse models by controlling key genes in fatty acid oxidation and glycolysis.[90]

Concluding remarks

Hyperinsulinemia is becoming recognised as an independent risk factor for chronic disease, yet there are few studies that address its management. This review evaluated hyperglycemia management methods, including physical activity, diet, and medications while focusing on the mechanisms of hyperinsulinemia as summarized in Table 1. First-line treatment of hyperinsulinemia should encompass dietary and physical activity management. Physical activity should include a combination of aerobic and resistance activities, with an emphasis on HITT. Care is needed to avoid over-training, which may exacerbate insulin resistance. Further research is needed to understand how to obtain the optimal balance. With respect to diet, a carbohydrate-restricted Mediterranean diet theoretically confers greatest benefit but further research is needed, especially to determine to what degree carbohydrates need to be restricted in relation to the degree of hyperinsulinemia. Although metformin may up-regulate GLUT4, pharmacological management is not currently justified due to the risks of cellular nutrition overload. Overall, strategies should aim to maximize participant adherence for greatest health benefits.

Conflict of interest

None Declared.

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