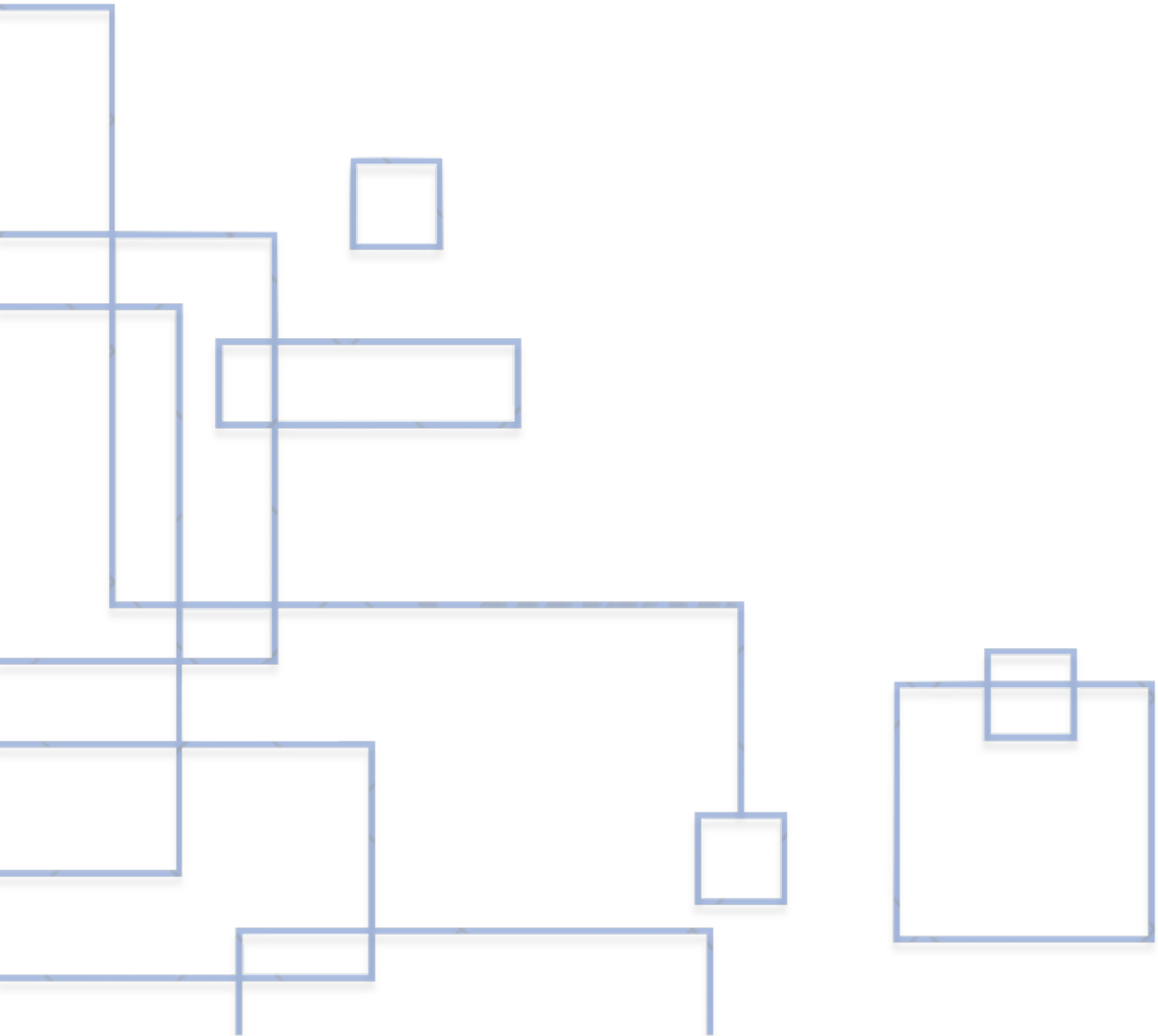
Prodromal Diabetes Mitigation and Prevention Strategy

Dr Catherine Crofts - 2024



Executive Summary

"The best time to plant a tree is 20 years ago.

The second-best time to plant a tree is now."

Chinese proverb

Current forecasts predict that in 2050, diabetes mellitus (diabetes) will affect 10% of the population, equating to 1 billion people worldwide. Of these, the majority will be diagnosed with type 2 diabetes (T2D) while part of the labour force. For each decade that a person has T2D, it is projected that they will lose 3.5 years of life, while the impact on morbidity remains unknown. However, T2D related morbidity will significantly impact society by placing a substantial burden on the health and welfare systems, while potentially reducing available funding via diminished human capital.

The absurdity of this situation is that the majority of T2D cases are believed preventable. Current research and isolated pockets of clinical practice have shown that appropriate lifestyle management of T2D can induce *remission* (defined as HbA1c below 48 mmol/mol without medication, except for metformin). Therefore, if we can induce remission, surely the same lifestyle practices would *prevent* T2D if applied sufficiently early? But the even bigger question is why is society not already demanding these strategies?

For a variety of reasons, medicine has worked with a glucocentric model for all forms of diabetes mellitus for hundreds of years. The belief that hyperglycaemia was the cause of all diabetes complications issues led to the adoption of the "euglycaemia should be maintained *at all costs*" treatment model. This model was rocked in 2008 when the ACCORD trial, which aimed to show that tight glycaemic control in people with T2D would reduce cardiovascular deaths, had to be halted early. Those in the intervention group had an unexpectedly high number of cardiovascular deaths compared to the control group *despite* greater improvements in glycaemic control.

Insulin is a pleiotropic hormone and has diverse physiological effects beyond its primary role in glucose metabolism and energy storage. Every cell in the body has insulin receptors, despite many of them (e.g. neurons) not requiring insulin for glucose uptake. This demonstrates how vital insulin is to the body. For example, people with sub-clinical or poorly managed type 1 diabetes (T1D), risk osteopenia, growth and developmental delays, and cognitive dysfunction - even in the absence of frank hyperglycaemia. However, insulin also has an under-recognised but narrow 'therapeutic window', where an excess also causes damage to many different body systems.

Insulin resistance has long been recognised as a prodromal phase of T2D and was also considered a key part of metabolic syndrome. However, there were several significant associated challenges. Firstly, there was no reference interval, or clinically useful diagnostic test. Even if testing was conducted, it did not change treatment protocols - therefore, testing was never recommended. Furthermore, there

was a fundamental lack of understanding as to why “the inability of the body to dispose of glucose” was mechanistically associated with the pathological states associated with insulin resistance.

When you consider insulin resistance and hyperinsulinaemia to be “two sides of the same coin”, then the epidemiology and mechanisms of “insulin resistance” become understandable. Insulin resistance can be simply described as “the inability of the cell to respond to normal amounts of insulin.” The body’s physiological approach to overcome insulin resistance is to secrete a higher or ‘compensatory’ amount of insulin, i.e. hyperinsulinaemia. Therefore, the two conditions co-exist, especially following carbohydrate consumption, so are frequently conflated. However, only certain cells within the body become insulin resistant - especially hepatocytes and myocytes. Other cells remain insulin sensitive, except they are now subject to supraphysiological insulin levels and so respond accordingly to these signals.

Hyperinsulinaemia can have many direct pathological effects on different body systems including: vascular (promotes atherosclerosis, hypertension, vasoconstriction, and prevents fibrinolysis); skeletal (decreases collagen quantity and affects mineral deposition); and increased overall oxidative stress and systemic inflammation. Furthermore, as insulin promotes cellular growth and division and has many mitogenic effects, hyperinsulinaemia has many oncologic effects.

The other challenge with the insulin resistance / hyperinsulinaemia paradigm is that the direction of causality is generally unknown and can be bidirectional. Chronic hyperinsulinaemia at the myocytes is recognised to down-regulate the GLUT4 transporters, which causes insulin resistance. Furthermore, excessive carbohydrate consumption in an insulin resistant person will trigger hyperinsulinaemia. This means that understanding the aetiology of insulin resistance / hyperinsulinaemia is complex. Many factors associated with modern living contribute to insulin resistance including: over-nutrition, poor sleep, circadian rhythm disturbances, stress, insufficient physical activity, and pollution.

Insulin resistance / hyperinsulinaemia - from here referred to as ‘prodromal T2D’- may slowly develop and be present for more than 20 years prior to the development of hyperglycaemia. Although this time-period represents an ideal intervention window to prevent T2D and/or other sequelae, identifying those with prodromal T2D is more complex as current measures for assessing insulin resistance have either insufficient precision, lack of association with long-term consequences, or are impractical.

Instead, to determine those with prodromal T2D, consideration should be given to associated signs and symptoms, where there is a known relationship with insulin resistance and/or hyperinsulinaemia. For example, all oral steroids (e.g. prednisone) are fundamentally known to cause insulin resistance. Therefore, all people prescribed long-term oral steroids should be considered insulin resistant, and therefore, prodromal T2D by default, with appropriate lifestyle management implemented to mitigate the effects of the steroid. Further clinical testing for insulin resistance may not be beneficial for these people.

Prodromal T2D may be presumed in other people. For example, primary hypertension is now considered to result from insulin resistance / hyperinsulinaemia

via insulin's role in mediating vasodilation and renal sodium management. Therefore, it is likely that people with primary or idiopathic hypertension also have prodromal T2D. Confirmatory clinical testing may not add value for this group but may be beneficial for monitoring.

The group where prodromal T2D clinical screening may be most beneficial are those at increased risk for developing T2D, but who are currently asymptomatic. For example, screening people for prodromal T2D 10 years earlier than the recommended age for screening for *diabetes* may help prevent many metabolic diseases due to earlier implementation of effective mitigation strategies.

Screening strategies can vary depending on the required degree of fidelity. For example, the current 'gold standard' test for insulin resistance is the hyperinsulinaemia-euglycaemic clamp test. However, this test is costly, complicated, has a high risk of complications, and the outcomes have not been consistently associated with clinical outcomes. By contrast, a one-off capillary blood test that concurrently assesses glucose and beta-hydroxybutyrate (BHB), can be easily performed in many primary care settings or even self-administered. While this test uses proxy markers for insulin, the test simplicity with recommended management strategies makes it easy and fast to implement.

People with indeterminate results, or those who respond poorly to management strategies could consider having an oral glucose tolerance test that concurrently measures, then maps, plasma glucose and insulin, and potentially BHB. Known as 'Kraft testing' this protocol is more expensive and invasive, however the interpretation of the resulting metabolite patterns or 'maps' can potentially better identify the underlying pathologies or suggest different management strategies.

Management strategies for prodromal T2D focuses on personalised lifestyle change that restores metabolic flexibility. Although nutrition and activity changes can have the greatest overall impact on improving prodromal T2D, many people 'fail' in making change when they address these first. For example, people often need assistance with stress, sleep, time or financial management, or education, before they can address nutrition or activity.

Blood markers, especially glucose and BHB need to be monitored frequently to assess the restoration of metabolic flexibility. There are many self-care test kits that are inexpensive and use capillary blood sampling with a point-of-care meter. There is increasing emphasis on the use of continuous monitors for both glucose and BHB as these allow for real-time tracking and are far less invasive than other methods.

It is becoming increasing recognised that many people, who want to improve their health "tangata whaiora", are unable to do this alone, and there is a significant gap in the New Zealand primary and preventative health care systems to provide adequate support. Health coaches, an emerging group of health professionals, are the necessary expertise in this space. By personalising behaviour change, health coaches will become indispensable in the intradisciplinary primary health care team, as they are able to spend more time with tangata whaiora to help them achieve their goals.

With time and implementation of these mitigation strategies, it is plausible to consider that the proposed lifestyle strategies for mitigating the effects of prodromal T2D will become key *preventative* practices. With even more time, it is hoped that

these lifestyle changes will just become cultural norms. To achieve the latter will likely involve not just individual change, but also legislative and other policy changes.

Overall, T2D is causing a global crisis, but is essentially preventable. Identifying and providing personalised management strategies to people in the prodromal phase of T2D will mitigate the looming public health and economic burden. People in this prodromal phase can be identified by either clinical history, signs or symptoms, or by a simple screening test that can be performed in primary care. Management strategies revolve around lifestyle changes, but many tangata whaiora may need personalised assistance to achieve the necessary changes. Health coaches are ideally suited to provide this assistance. With time and cultural change, it is hoped that the mitigation strategies morph to become preventative strategies, and further to become normal culture. High-level policy changes will catalyse embedding of healthy lifestyles into culture. We must plant the seeds of change.

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Overview

The global tsunami of non-communicable diseases is about to hit breaking point. The prevalence of obesity, non-communicable diseases, and their sequelae are increasing with such magnitude that without international implementation of effective prevention and mitigation measures, widespread suffering will prevail. In the USA, it is estimated that less than 1 in 8 adults have optimal metabolic health (1). Within New Zealand, most people die from a non-communicable disease (Figure 1). Although only a small proportion of people die directly from diabetes (3%), a diagnosis of T2D significantly increases the risk of developing many cardiovascular disorders and certain cancers or dementias. This means that understanding the root cause of T2D will not only benefit those with the condition, but also those with many other non-communicable diseases from metabolic origins (known as metabolic disorders).

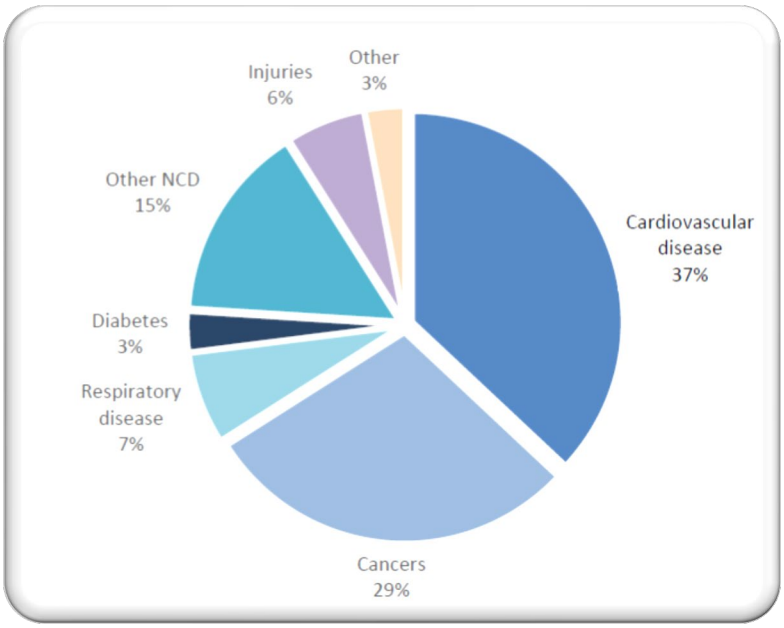


Figure 1: Proportion of all-age deaths in New Zealand, 2008

Diabetes

The traditional definition of diabetes mellitus is a disorder of the pancreas, resulting in a deficiency of insulin, causing hyperglycaemia. For example,

- **"Diabetes** is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces." (World Health Organization)
- "**Diabetes** is a disease where your body cannot control its blood sugar levels properly - either because your body doesn't make enough (or any) insulin, or because your cells have become resistant to insulin." (NZ Ministry of Health)
- "**Diabetes mellitus**, [a] disorder of carbohydrate metabolism characterized by impaired ability of the body to produce or respond to insulin and thereby maintain proper levels of sugar (glucose) in the blood. (Britannica)

Yet diabetes mellitus, often called simply 'diabetes', is actually a spectrum of disorders of the pancreas characterised by *anomalies* in insulin secretion leading to the common symptom of excessive glucagon secretion (hyperglucagonaemia) leading to hyperglycaemia. There are many different types of diabetes, but this report will concentrate on the four main types: type 1, type 2, gestational, and monogenic diabetes. Table 1 highlights the differences between these sub-types.

With T1D, the anomaly is insulin insufficiency, generally caused by autoimmune destruction of the beta cells of the pancreas. This normally occurs before the age of 25 years, and first-line treatment is exogenous insulin. This led to alternative names of "juvenile onset diabetes" or "insulin-dependent diabetes".

T2D is still often considered ‘insulin insufficiency’ with the implication that the body requires more insulin due to the underlying insulin resistance. Yet, as will be discussed later, the failure of cells to respond to normal levels of insulin (“insulin resistance”) results in *compensatory hyperinsulinaemia.*

Gestational diabetes is diabetes mellitus of any subtype first diagnosed during pregnancy. If the hyperglycaemia does not resolve in the post-partum period, then the diabetes is reclassified into the appropriate subtype and care transferred.

Monogenic diabetes has a clear genetic aetiology involving a single gene mutation. There are multiple variants which are often clustered into neonatal diabetes, or ‘maturity onset diabetes of the young’ or ‘MODY’.

These four main types of diabetes have clearly distinct aetiologies which lead to different disease progression, sequelae, and treatment strategies although there is often considerable overlap, especially with the latter three types. There are also different prevalence rates with different ethnic populations, although considerable work is needed to determine ‘nature from nurture’.

Over the last ten years understanding of the underlying pathophysiology of T2D has increased. When combined with the established treatment methodologies used by isolated clinicians and recent innovative technologies, pragmatic management strategies can be developed to allow wide-spread implementation. The challenge is that many of these ‘pragmatic management strategies’ are contentious as they tend to contradict current clinical protocols. Following acceptance at policy level, ‘contentious’ strategies are easier for many clinicians to adopt as they have support at the management level for their decisions.

The aim of this document is to provide an overview of T2D, with a focus on its prodromal state - insulin resistance. By understanding the aetiology and pathophysiology of insulin resistance, and its counterpart ‘hyperinsulinaemia’, the strategies to prevent the progression towards T2D are clear.

Table 1: Summary of the four main types of diabetes mellitus

	Type 1	**Type 2**	**Gestational**	**Monogenic**
Definition	Pancreatic beta cell deficiency hypoinsulinaemia & hyperglucagonaemia	Insulin resistance, hyperinsulinaemia & hyperglucagonaemia	Hyperglycaemia first diagnosed during pregnancy	Diabetes resulting from a single gene mutation. Usually includes neonatal diabetes and Maturity Onset Diabetes of the Young (MODY)
% of occurrence	5-10%	90-95%	10-25% of pregnancies	0.001-5%
Age of onset	Children/teens most commonly affected, but some forms of T1D may occur at any age (e.g. LADA)	Adults (> 40 years) at highest risk but may occur at any age	Linear relationship with increasing age (for each one-year increase in maternal age, risk increases by 7.9%)	< 6 months, likely neonatal diabetes MODY typically diagnosed between puberty – 35 years
Aetiology	Considered to be autoimmune disease triggered by an environmental factor superimposed on polygenetic predisposition	Lifestyle and environmental factors superimposed on polygenetic predisposition	Believed to be normal pregnancy physiology superimposed on subclinical insulin resistance and hyperinsulinaemia	Monogenic, but multiple gene variants
Speed of onset	Traditionally thought to be rapid (days to weeks), some evidence suggesting can take up to 5 years	Gradual (years to decades)	Unknown, usually detected about 24-28 weeks of pregnancy	Present at birth, but may not be symptomatic

Body habitus	Thin to normal	Normal to obese	Normal to obese	Varies
Therapy goals	Mitigation	Prevention - Remission	Prevention-mitigation[1]	Mitigation
Treatment	1. Insulin injections 2. Lifestyle management 3. Oral hypoglycaemics e.g. metformin	1. Lifestyle management 2. Oral hypoglycaemics 3. Insulin injections 4. Bariatric surgery	1. Lifestyle 2. Metformin 3. Insulin	1. Lifestyle 2. Pharmacological therapy depends on gene variant.

[1] While parturition can appear to 'cure' gestational diabetes in most cases, approximately 50% will later develop type 2 diabetes

Type 2 diabetes

Epidemiology

The historical prevalence of diabetes is not known, however was generally described as being 'rare' in preindustrial times (2). It is likely that many cases of T1D sickened and died without ever seeing a physician who knew about diabetes. Given the lack of effective antibiotic treatment and long prodromal phase, people with T2D likely died from sepsis long before any polyuria became overt.

It is currently recognized that the prevalence of diabetes is increasing in both global and New Zealand terms and is influenced by multiple factors, including ethnicity, epigenetic, and socioeconomic factors. While many sources cannot distinguish between the different types of diabetes, generally gestational diabetes is not included in these statistics and monogenic diabetes is usually included with T2D statistics.

By the 1960s, the global prevalence of diabetes was estimated to be 2% of the total population, with one source estimating T1D comprising about 20% of these cases (2). Currently the global prevalence of diabetes is approximately 6% and is projected to increase to > 10% by 2050 (3). Almost all this increase is projected to be T2D, which currently comprises about 90-95% of all cases.

Given that the global population in the 1960s was approximately 3 billion, is currently 7.5 billion and predicted to be nearly 10 billion by 2050, these percentages translate from 60 million people affected worldwide in the 1960s to 1 billion people in 2050: a 16-fold increase in less than 100 years.

In New Zealand in 2022, approximately 4.3% of the population had a diagnosis of diabetes (subtype not specified), an increase from 3.6% over the last ten years. This can be broken down by ethnicity, with Pasifika people having the highest prevalence of 12%, Indian at 10%, Māori at 7%, and European/other at 3%. The overall low prevalence rates can be explained by the difference in total numbers of people within each group (4).

Age at diagnosis trends

It is of increasing concern that the average age at diagnosis for T2D is decreasing. The NHANES III study, which covered from 1988-1994, had a mean age at diagnosis of 52 years. This decreased to 46 years for the NHANES study (1999-2000) (5). While there is a paucity of recent studies reporting age at diagnosis in a comparable way, it is now estimated that more than 16% of global T2D cases are younger than 40 years of age at the point of diagnosis ("young-onset T2D") (6). There are also noticeable trends in youth data. A large study in the USA showed a 31% increase in the prevalence of T2D in youths under 20 years. Of particular concern were the overrepresentation of the female sex and the increase in all ethnicities except non-Hispanic White (7). In the Waikato and Auckland regions, 25% of youths and young adults aged < 25 years had T2D with the majority from Māori or Pasifika ethnicities (8).

This younger age at onset is of significant concern for a multitude of reasons. Disease progression is more rapid in those with young-onset T2D ($T2D_{YO}$) and there is a higher risk of diabetes related complications compared to a similar age at diagnosis with T1D. This confers considerable risk to the labour force and economic base of any nation. For example, the risks of retinopathy or neuropathy increase with disease duration (7, 9). The maternal uterine environment is considered a risk factor for $T2D_{YO}$ (7), therefore the overrepresentation in the female sex confers further risk for future generations.

Furthermore, it is currently estimated that every decade lived with T2D is associated with a 3–4-year loss of life expectancy compared to someone without diabetes (10). This means a 20-year-old with T2D could have 15 fewer years of life compared to someone diagnosed at 60 years of age.

Socioeconomic factors

There is a significant debate as to whether 'nature or nurture' is responsible for the increased prevalence of diabetes, especially type 2. This may be explained by epigenetics - or the factors that explain changes to gene expression but does not directly involve changes to the DNA sequence (from the Greek 'epi' meaning 'in addition to'). Behavioural or environmental factors can influence which genes are expressed. This means that a person may have genetic susceptibility to developing a condition, but it takes another factor, especially environmental, before that gene will be expressed to a degree that the condition develops. For example, certain ethnicities had a very low rate of diabetes prior to Western colonization. However, after adopting a Western lifestyle, especially a standard American diet (SAD), their rates of diabetes, especially type 2, show dramatic increases. It is hypothesized that the change in diet causes epigenetic changes that increase the expression of certain genes that accelerate the development of T2D compared to other ethnicities, especially European.

Socioeconomic factors are well-recognized at contributing to the prevalence of diabetes. People with higher household income are more likely to have time for physical activity and access to public open spaces, have better access to healthy food, less likely to consume ultra-processed foods, less likely to work evening or night shifts, and less likely to smoke - all factors known to reduce the risk of diabetes and other metabolic disorders. In New Zealand, this is shown by a prevalence of diabetes of 2.7% for those living in the least deprived areas, compared to 7.2% for the most deprived areas.

Te Tiriti o Waitangi

From a Te Tiriti o Waitangi perspective, New Zealand needs to urgently address T2D, especially $T2D_{YO}$. Tangata whenua are disproportionately affected by diabetes overall compared to the non-Māori population. Furthermore, tangata whenua are disproportionately affected by T2D compared to the European population (11). Although there are many factors that contribute to the higher rate of prevalence of T2D in tangata whenua, strategies that prevent or mitigate the risks of the T2D in this population will be translatable to other populations within New Zealand and will likely translate to our South Pacific whānau and assist in global strategies.

Insulin Resistance

Insulin resistance can be simply defined as the inability of the body's cells to respond to a physiologically normal level of insulin. However, "insulin resistance" is a poorly defined concept that aims to explain the aetiology and pathophysiology of T2D. To understand insulin resistance, it is important to first understand the role of insulin.

Insulin

Insulin is a polypeptide hormone produced by the β-cells of the pancreas. Although its effects on glycaemic regulation are well established, insulin has multiple roles within the body. Insulin receptors are found in every body cell type – even in those that are independent from insulin for glucose uptake.

Insulin works in concert with many other hormones, including glucagon, cortisol, and noradrenaline, and body processes that regulate blood glucose levels. Actions such as eating, resting, physical or mental activity or stress, temperature fluctuations, injuries or illness can all exert different hormetic effects that change the requirement for systemic glucose. Both excessive and insufficient blood glucose has detrimental health effects. As insulin is the only hormone that will actively lower blood sugar levels, it plays a key role in maintaining glucose's narrow therapeutic window.

Insulin is released from the pancreas in a basal / bolus response to maintain homeostasis as shown in Figure (12). It is currently hypothesized that basal release processes occur when blood glucose levels are below ~5 mmol/L (12). Basal insulin secretion of ~0.25-1.5 units of insulin per hour is believed to account for approximately 50% of total daily insulin of a healthy person (13). The pulsatility nature of basal insulin release are associated with ultradian body processes while also reducing the risk of downregulating insulin receptors – a key process in the development of insulin resistance.

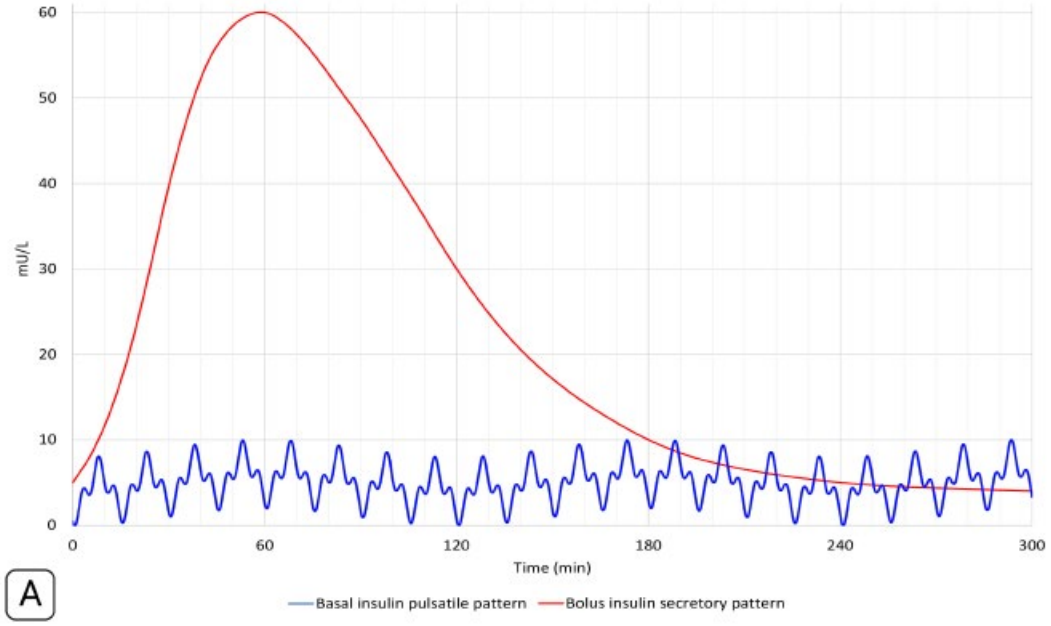


Figure 2: Basal/Bolus insulin release from Cooper et al (12)

Bolus release of insulin is triggered when blood glucose levels rise above approximately 5-6 mmol/L. Glucose entering the pancreatic beta cells generate sufficient ATP to cause a rapid exocytosis of insulin ("first phase" insulin response). If the blood glucose remains elevated, other secretagogues induce and sustain the "second phase" of insulin response (Figure 3). The first phase insulin response is brief (< 10 min) so is often undetected (14). Defects in first phase insulin response are recognised to be early indicators for both T2D (14) and T1D (15) and may occur up to years before detectable hyperglycaemia.

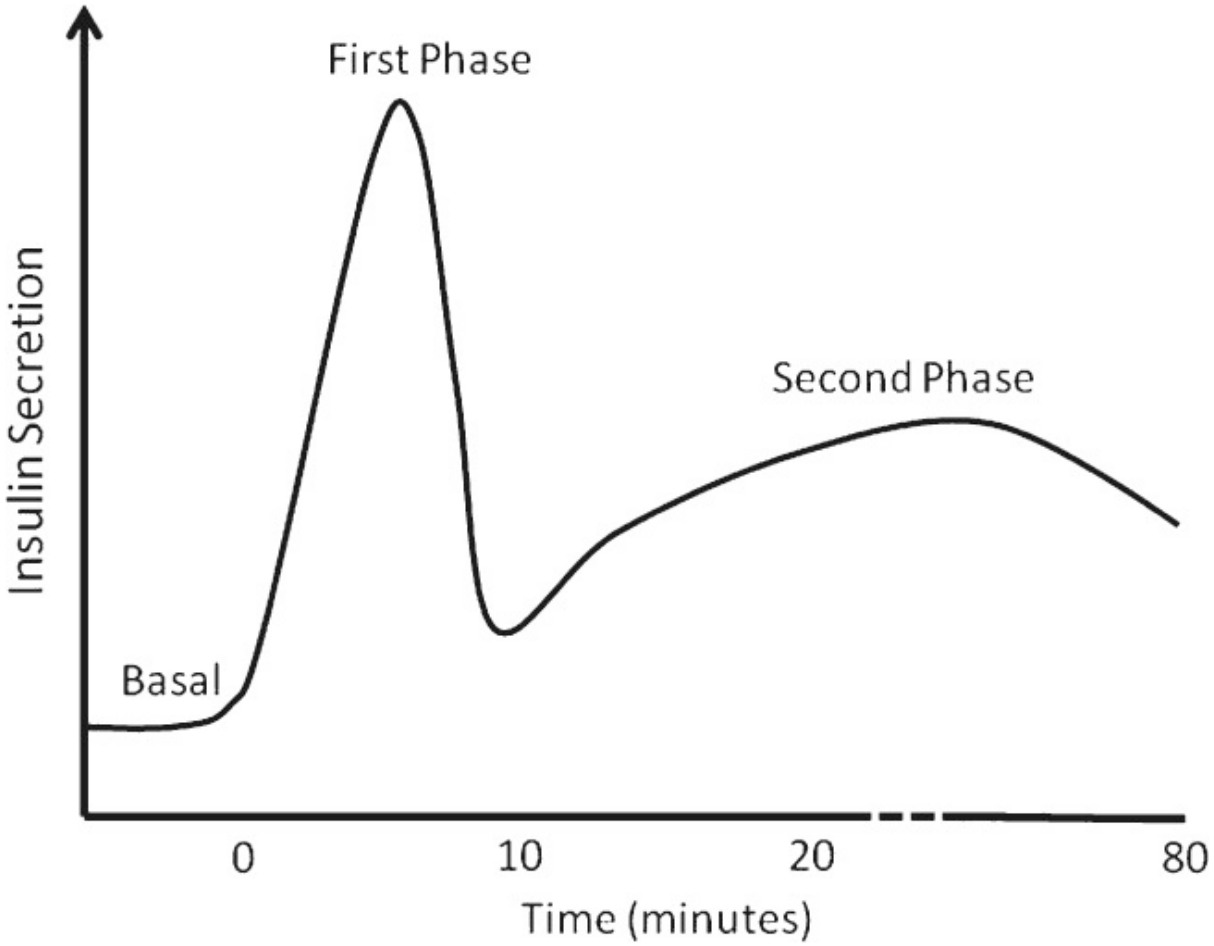


Figure 3: Conceptual model of biphasic insulin secretion in response to a glucose bolus.

Energy storage functions of insulin

Although many sources will describe insulin's main action as allowing glucose to enter cells to be used as energy, this description is extremely simplistic. Firstly, every cell within the body contains the glucose transporter type 1 (GLUT1), which is an insulin *independent* transporter that allows all cells to uptake glucose in the absence of insulin. The insulin *dependent* transporter is GLUT4, found predominantly in muscle and adipose tissues. Muscle will absorb 80% of postprandial blood glucose (16) and this is an important protective mechanism when blood glucose rises above 6 mmol/L. Excessive blood glucose will bind to proteins (glycated proteins) damaging them. Reducing exposure time to hyperglycaemia prevents a lot of metabolic damage. As glycaemia increases, insulin is released from the pancreas, upregulates the GLUT4 transporters, which rapidly restores glycaemic control. Glucose taken up by myocytes is either used immediately to generate ATP in the

mitochondria or stored as glycogen. Ideally ATP is generated via oxidative phosphorylation as this is the most energy efficient process and generates the least oxidative stress.

As myocytes have a limited capacity for glucose uptake, insulin concurrently upregulates adipose GLUT4 transporters stimulating lipogenesis and inhibiting lipolysis, which has the follow-on effect of inhibiting hepatic gluconeogenesis (17). Finally, as part of storing energy, insulin also upregulates hepatic glycogenesis (Figure 4). Overall, incoming glucose that is not required immediately as energy is stored as glycogen or fat.

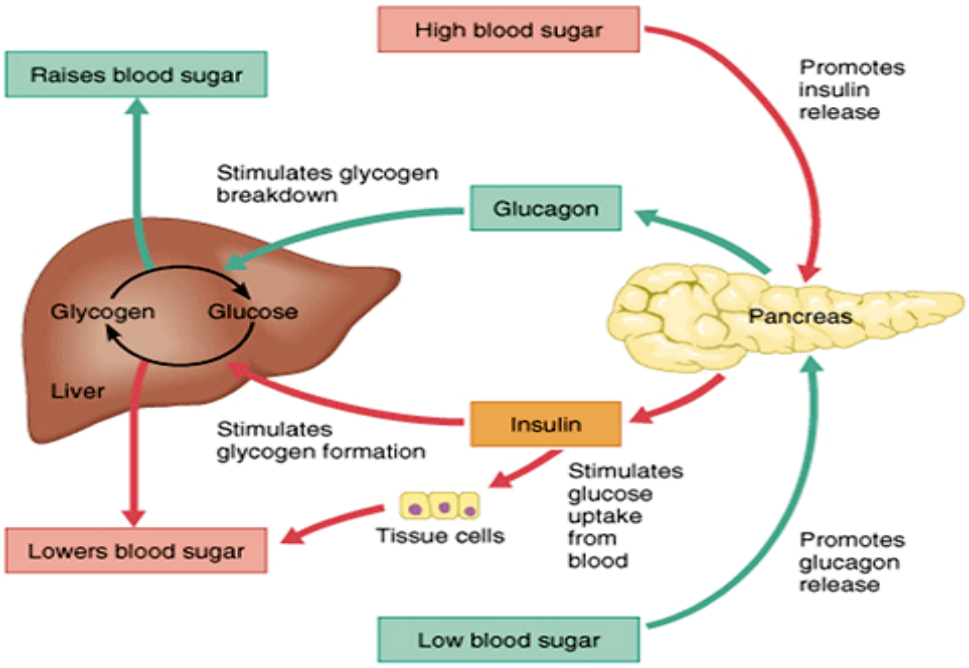


Figure 4: Complementary roles of insulin and glucagon

Insulin Resistance

The challenge with insulin as an energy storage hormone is what occurs when energy intake, especially in the form of carbohydrates, exceeds the body's storage capacity. Typically, if a person eats an isolated macronutrient (protein, fat, carbohydrate), appetite self-regulates, so it is difficult to eat an excessive amount. However, when fat and carbohydrates are eaten together, this appetite regulation is over-ridden, leading to excessive consumption. Milk is the only food found in abundance in nature that contains relatively high amounts of both fat and carbohydrate. As milk has evolved to promote growth in infants of all mammalian species, this suggests that there are evolutionary benefits to this phenomena. However, the same phenomena in grown adults can be detrimental.

Excessive caloric consumption (overnutrition) causes a prolonged post-prandial hyperglycaemia (6-10 mmol/L). As the myocytes approach glucose capacity, GLUT4 no longer translocate to the cell surface with the intent of preventing excessive glucose uptake and subsequent risk of cellular damage. Essentially the myocyte has become "insulin resistant" as it is no longer responding to normal plasma insulin concentration.

If the post-prandial hyperglycaemia is sustained, then there is additional pressure on the pancreas to secrete more insulin. This may result in both a heightened and prolonged period of insulin secretion. This hyperinsulinaemia can overcome the myocyte insulin resistance by forcing GLUT4 translocation. Although the hyperinsulinaemic process does

risk oxidative stress in the myocytes, it will also stimulate further lipogenesis. If necessary, hyperinsulinaemia can also stimulate extra fat storage capacity via both hypertrophic and hyperplasic processes (Figure 5).

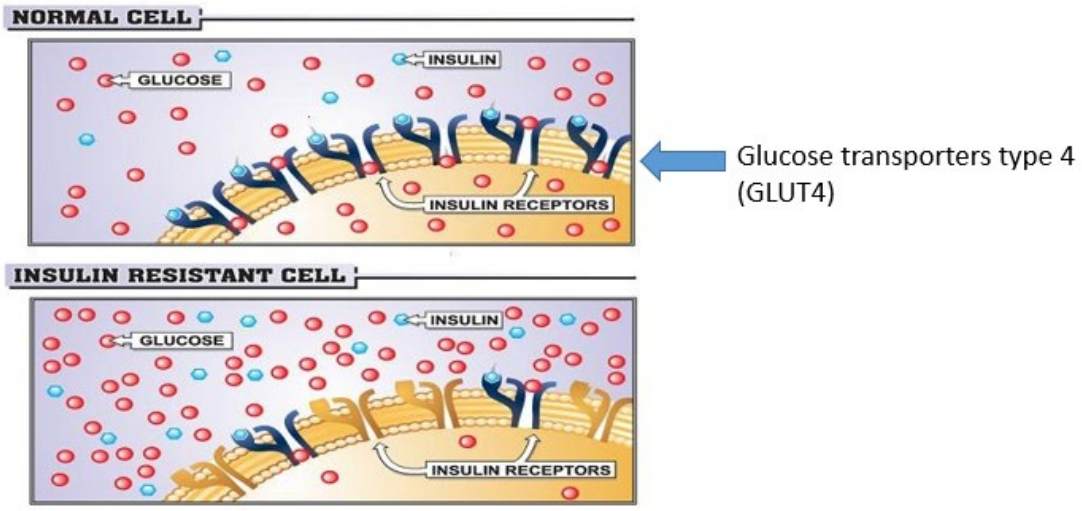


Figure 5: Concept image of insulin resistance causing hyperinsulinaemia

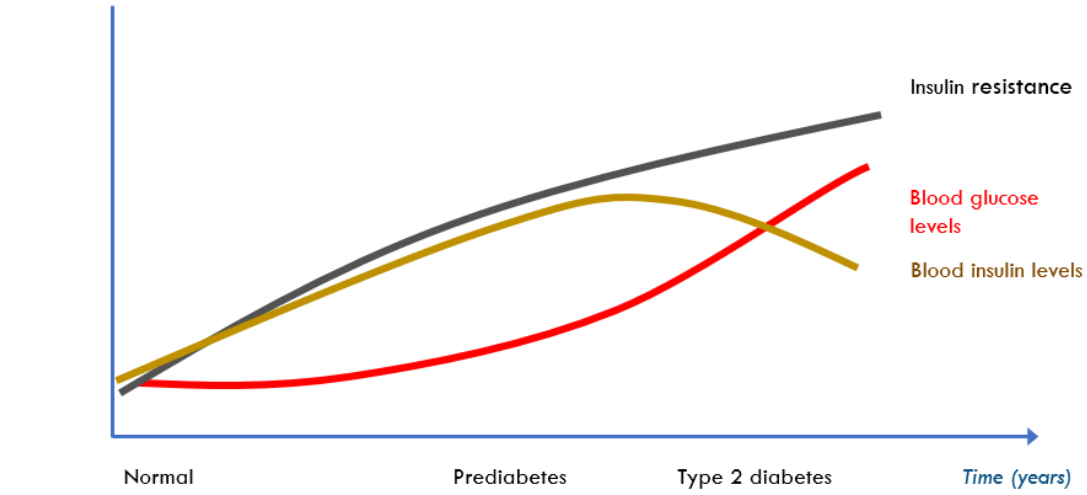
While overnutrition is the most common cause of insulin resistance, there are other mechanisms. Excessive cortisol, from stress, illness, or inadequate sleep, will also down regulate GLUT4 transporters. It is hypothesised that the resulting hyperinsulinaemia and hyperglycaemia mitigated injury-related consequences and/or allowed greater short-term resilience.

Acute, transient insulin resistance is normal and an important part of human evolution. For example, insulin resistance and subsequent compensatory hyperinsulinaemia is important during periods of growth or anticipated starvation. For example, insulin resistance occurs during both puberty and pregnancy as it ensures rapid nutrition sequestration and supports growth factors. Acute insulin resistance could also be considered an evolutionary measure to ensure adequate fat stores to protect against an upcoming fast (e.g. autumn before winter, or in traditionally hunter-gatherer populations).

Generally acute insulin resistance is followed by an appropriate time/environment for recovery, e.g. autumn is followed by winter, pregnancy is followed by breast-feeding. The subsequent catabolic processes restore health by repairing cells damaged by oxidative stress and by rectifying adipose capacity.

In the modern world, factors that predispose towards insulin resistance are more common, including prolonged stress, overnutrition, or inadequate sleep. Inadequate physical activity, which diminishes myocyte glucose storage capacity, exacerbates the risk of insulin resistance.

Acute insulin resistance is transient and a normal, cyclical, aspect of human physiology. With adequate recovery, baseline insulin sensitivity (the antithesis of insulin resistance) is restored. Prolonged insulin resistance loses the transitory nature for unknown reasons and becomes chronic. This causes increased metabolic stress and predisposes the person to metabolic diseases. T2D is the mostly widely recognised consequence of this process as depicted in Figure 6.



Adapted from Henry (1998) doi: 10.1016/S0002-9343(98)00207-1

Figure 6: Conceptual depiction of the natural history of type 2 diabetes

The biggest misnomer in this process is to describe the person as being "insulin resistant." Only certain cells become insulin resistant, especially the liver, muscles, and fat cells i.e. the glucose storage cells. However, as insulin is a pleiotropic hormone, and has diverse effects on different cells, the effects of the compensatory hyperinsulinaemia need to be considered.

Hyperinsulinaemia

Hyperinsulinaemia is the under-recognised counterpart to insulin resistance. As depicted in Figure 5, when someone is insulin resistant, compensatory hyperinsulinaemia will occur to correct hyperglycaemia. This results in supraphysiological levels of insulin. As the non-glycaemic effects of insulin are poorly understood, the significant physiological consequences have also been overlooked.

As previously stated, insulin receptors are found on every cell in the body despite many not requiring insulin for glucose uptake. Once bound to an insulin receptor, insulin activates many biochemical pathways mostly via IRS-1, PI3K, AKT, and mTOR. These biochemical pathways are key for the many different metabolic processes including cellular differentiation, growth factor signalling, protein synthesis and cell growth, cell migration, angiogenesis, neuronal growth, survival and neuroplasticity, and apoptosis inhibition.

Simplistically, insulin supports and encourages cellular growth and repair. This means that hyperinsulinaemia is important during times of puberty, pregnancy, and illness/injury recovery. However, if excessive, or prolonged, it leads to many deleterious effects as summarised in Table 2.

For example, hyperinsulinaemia is implicated in the development of many cancers both directly and indirectly. By preventing apoptosis, precancerous or cancerous cells may not be removed by the body. Insulin supports cellular growth and proliferation via a variety of factors, both direct and indirect, such as increased angiogenesis, thus supporting the cancer. Finally, insulin encourages cellular migration, which can contribute to metastases. T2D, a hyperinsulinaemic state, is a well-known risk factor for a variety of cancers.

Table 2: Summary of biological systems and disease states affected by hyperinsulinaemia (18)

Biological System	Disease	Mechanism
Cancer*	Breast, ovarian, colon, bladder, pancreas, liver	Increased IGF – increased growth and proliferation
		Decreased apoptosis
		Increased angiogenesis
		Increased glucose uptake and utilisation
		Increased production of reactive oxidative species
		Increased sex hormone production and decreased sex hormone binding globulin
		Inflammation
Circulatory	Atherosclerosis	Increased proliferation and migration of arterial smooth muscle cells
		Increased triglyceride formation
	Endothelial dysfunction (microvascular disease)	Changes to capillary permeability
		Vasoconstriction
		Inhibits fibrinolysis
	Cardiovascular: other	Suppressed ketogenesis
		Enhanced sodium resorption
Gastrointestinal	Diabetes: Type 2 and gestational	Prolonged insulin resistance eventuating in insulin demand exceeding supply – causing hyperglycaemia
	Non-alcoholic fatty liver disease	Lipogenesis exceeds distribution capacity
Endocrine	Chronic inflammation	Stimulation of mitogen-activated protein kinase pathway
		Increased cytokine production
	Obesity	Decreased lipolysis
		Lack of appetite suppression
Nervous	Alzheimer's disease	Changed regulation of beta-amyloid and tau protein
		Decreased synaptic plasticity caused by dysregulated PSA-NCAM** interactions
	Other central and peripheral neuropathies	Insulin resistance in the dorsal root ganglion neurons resulting in decreased Akt – needed for growth, development, maintenance, and survival
		Akt key for neuroplasticity and neuroprotection
Skeletal	Osteoporosis/osteofragalitis	Impairs new collagen synthesis
		Preferential differentiation of mesenchymal cells into adipocytes instead of osteoblasts or chondrocytes

*While cancer is not typically classified as a “biological system”, due to its recognition and impact as a key chronic disease, it was decided that it warrants a classification on its own, rather than be integrated into individual biological systems.

**PSA-NCAM = polysialic acid - neural cell adhesion molecule.

Metabolic inflexibility

Mitochondria are especially affected by hyperinsulinaemia leading to downregulated ATP production and impaired fatty acid oxidation as this allows for greater glucose disposal. The downsides to this are that this leads to a greater production of reactive oxidative species (ROS), which leads to premature aging, but also supresses ketogenesis. If the hyperinsulinaemia state is prolonged, then ketogenesis and fatty acid oxidation can be downregulated to the extent that the body becomes reliant on glucose as a fuel and simply cannot use fat to generate ATP; a state known as 'metabolic inflexibility'.

Comorbid effects

The mechanisms summarised in Table 2 may have different effects in different body systems, resulting in the different manifestations of metabolic disease as depicted in Figure 7. Often these conditions are treated by different departments in the New Zealand public health system, but they all stem from the same root cause. If conflicting advice is given for management, this may cause additional barriers for a return to health.

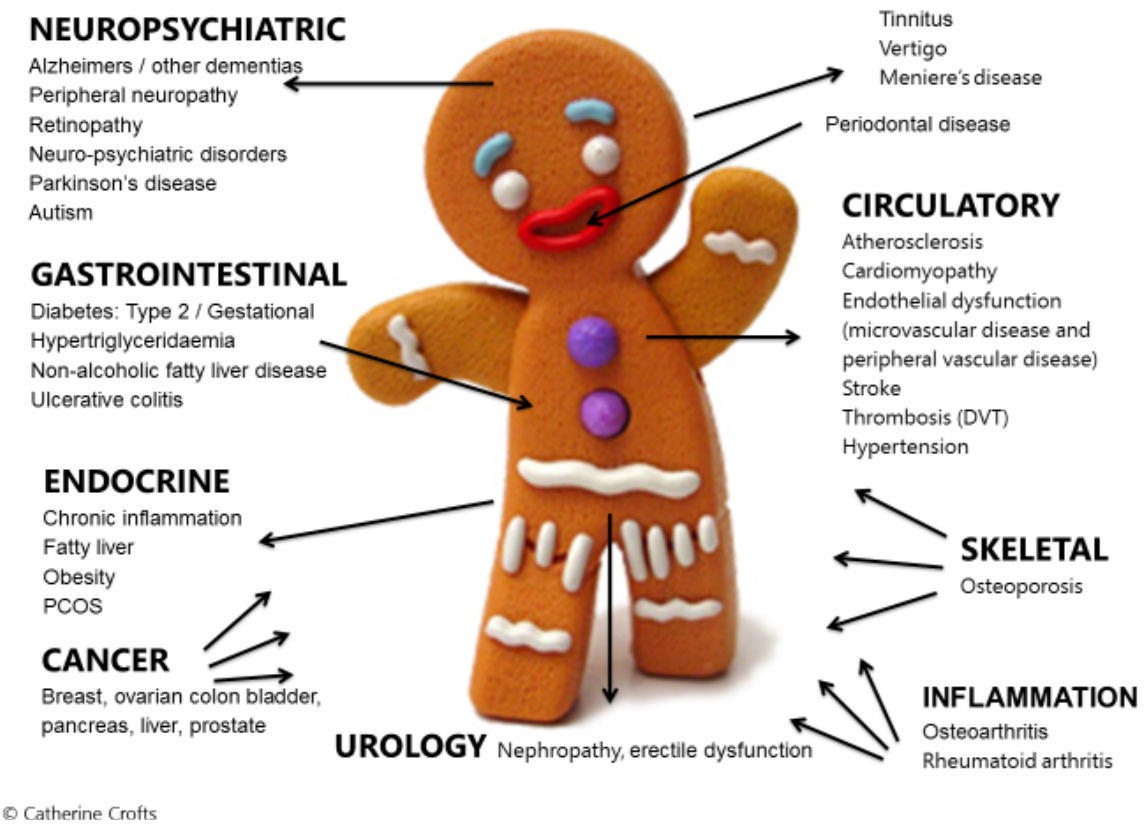


Figure 7: Systemic effects of chronic hyperinsulinaemia

When does hyperinsulinaemia occur?

In the absence of T1D, hyperinsulinaemia will always occur when the carbohydrate load exceeds the body's capacity to metabolise and distribute excessive glucose. The rate and extent of the hyperinsulinaemia will depend on many factors, including (but not limited to) basal metabolic rate, nutrition, physical activity, other hormonal influences, especially cortisol and glucagon, free fat mass, and basal insulin resistance rate.

An increasing challenge in society is "reactive hypoglycaemia" commonly known as being "hangry". Within a 2–4-hour period of carbohydrate consumption, the person becomes tired

and loses concentration, followed by increasing irritability, frustration and/or anger. These symptoms resolve through eating – especially simple carbohydrates. The underlying physiology is hypothesised to be decreased clearance of insulin, leading to prolonged insulin action, and *over-correction* of the postprandial hyperglycaemia resulting in hypoglycaemia. A lack of fuel in the central nervous system causes decreased concentration and fatigue. This causes adrenaline and noradrenaline to be released as part of an evolutionary survival mechanism, causing the mood symptoms. Although easily resolved with food, correcting reactive hypoglycaemia with simple carbohydrates risks cycle perpetuation.

Hyperinsulinaemia and insulin resistance

As explained above, hyperinsulinaemia and insulin resistance coexist and have a bidirectional causality. Hyperinsulinaemia downregulates insulin receptors hindering the translocation of GLUT4 to the cell surface, which causes insulin resistance. However, insulin resistance means post-prandial hyperglycaemia is prolonged, which results in increased pancreatic signalling and hyperinsulinaemia.

Prodromal diabetes

Any intervention that improves hyperinsulinaemia and/or insulin resistance will result in health improvements. One challenge is considering the best time to intervene. Currently, most medical and/or staged interventions occur when the person develops a metabolic disease. However, in order to be prevent / delay / mitigate metabolic disease, it may be more effective to intervene when a person is hyperinsulinaemic/insulin resistant but still normoglycaemic, described as the prodromal phase of diabetes as shown in Figure 8.

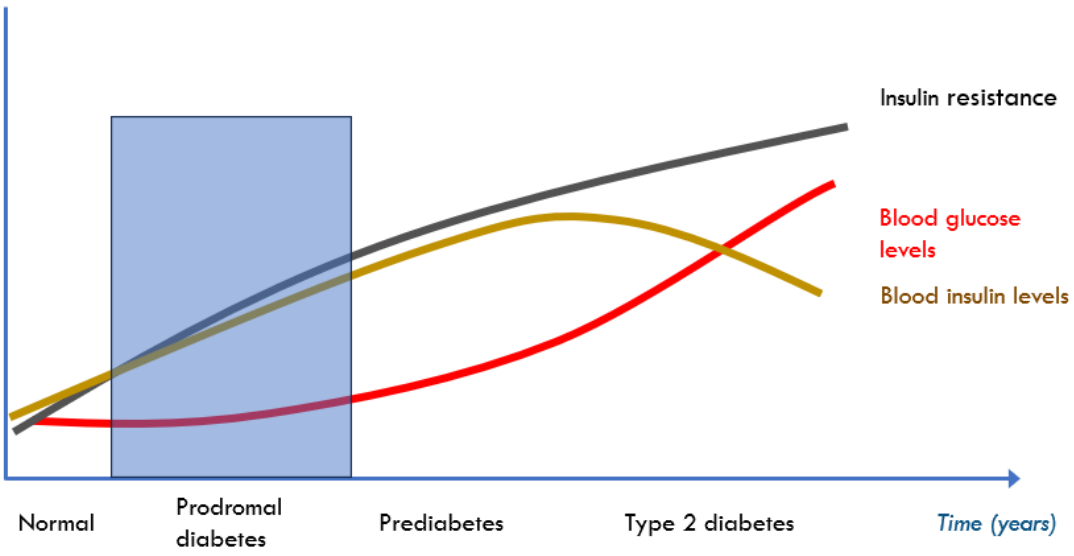


Figure 8: Prodromal phase of diabetes

This 'prodromal' phase of T2D may last up to 24 years and may be hard to identify as there are few overt symptoms. However, at minimum, there would be an absence of BHB in the presence of normoglycaemia (12), and a greater insulin response to an oral glucose challenge including a prolonged half-life of elimination (19).

Identifying prodromal diabetes

In the absence of any overt signs/symptoms of hyperinsulinaemia/insulin resistance, especially in people with increased risks of developing T2D metabolic testing could be considered.

Tests based on fasting insulin

It is a common assumption that fasting insulin will reliably identify the prodromal phase of T2D. However, this is not proven in practice despite being in common use in both clinical practice and research. HOMA variants are potentially the most common and are based on algorithms that use fasting insulin and fasting glucose. While these tests are useful for testing an intervention on a population basis (e.g. a clinical trial), they have significant flaws for individual monitoring due to the oscillatory nature of insulin secretion. Studies by Crofts et al. (20, 21) showed that fasting insulin levels have poor test-retest repeatability and can vary by 90-135% (Figure 9). Greater variation in insulin variability was noted in people with poorer glycaemic control. To detect clinical change on an individual level, fasting insulin needed to change by approximately 90%, equating to a difference of 6-8 mU/L of fasting insulin between subsequent tests.

There is no consensus for a reference interval for fasting insulin, although different institutes have their own guidelines. Applying the standard principle of using the mean of the healthy population, ± 3 standard deviations (SD) against the Kraft dataset gives a mean of 7 mU/L (SD = 5) for fasting insulin (19). Therefore, a reference interval of 0-22 mU/L could be considered a 'normal' fasting insulin.

People with prodromal diabetes had a mean fasting insulin of 11-16 mU/L with a standard deviation of ~9 mU/L (19). This means that fasting insulin is an imprecise marker as levels below 15mU/L cannot differentiate between healthy people and those with prodromal diabetes. However, there is reasonable consensus that fasting insulin levels above 20mU/L indicate hyperinsulinaemia.

If fasting tests are deemed necessary, it has been recommended that three samples are taken at 5 minute intervals and the mean of the three tests used to try and reduce the 'noise' from insulin's variability (21). Multiple samples are more expensive and, unless the result is greater than 22 mU/L, may still not differentiate between healthy and prodromal diabetes.

It is also suggested that frequent fasting insulin sampling (e.g. at least weekly) can help determine individual trends, and therefore clinical status. However, this not practical in the New Zealand context.

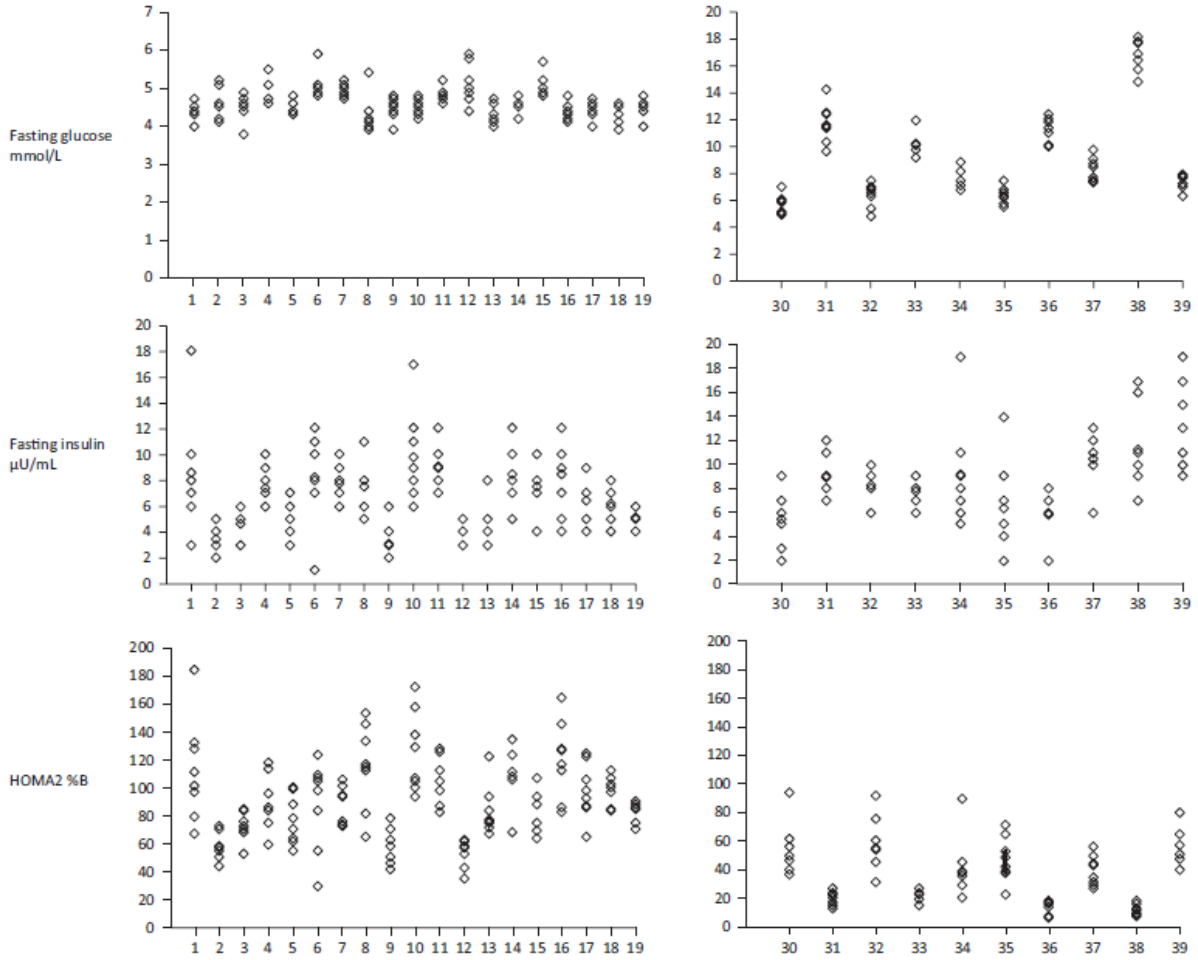


Figure 9: Raw data for control (left) and T2D (right) for fasting glucose, fasting insulin, and HOMA2 %B measures from Crofts et al (21)

Kraft patterning

Assessing an individual's post-prandial insulin response to a carbohydrate challenge could be considered the "gold standard" for understanding their insulinaemic status, however, this test is involved and resource demanding (19). The Kraft test, or Kraft patterning, is derived from the protocols developed by Dr Joseph Kraft, a pathologist in Chicago from the 1970s-1990s (22). Kraft collated a dataset of nearly 15000 tests[2] and accumulated more than 30 years of understanding insulin/glucose response patterns.

Firstly, the individual must undergo a 14-day preparation period where they consume at least 50g carbohydrates three times daily (150g/carb per day). Then the person needs to undergo a multi-sampled oral glucose tolerance test (OGTT) with insulin assays. Following an overnight fast, the person has a baseline plasma sample taken, then consumes 75-100g glucose in water. Subsequent samples are taken 30, 60, 120 and 180 min, potentially also at 240 and 300 minutes after the consumption of the glucose. Samples are quantified for insulin, glucose, and ideally BHB (23).

As depicted in Figure 10, healthy people display a glucose pattern that follows the WHO guidelines for normoglycaemia (24). Fasting insulin is relatively low, then increases to a low to moderate peak between 30-60 minutes and returns to baseline by 120 minutes. Increasing concentration magnitudes and/or elimination delays indicate progression towards

[2] The Kraft dataset is on permanent loan to Dr Catherine Crofts for non-commercial research.

prediabetes. By contrast, people with T2D may also have a relatively low fasting insulin, which increases to a high peak – usually at or after 120 minutes – with a slow and delayed rate of return to baseline.

While BHB was not an original part of the Kraft methodology, subsequent research has shown that in healthy people, ketone production is suppressed during the OGTT, but ketogenesis should return by 240 minutes. Delays may indicate progression towards prediabetes. Further research is needed to determine if this is a transient or irreversible condition.

Kraft patterning is recognised to be expensive and demanding on the participant. The multiple blood draws (at least 5 over three hours) is time demanding and requires significant mental fortitude (even if a cannula is used). Furthermore, during the test period, only additional water is permitted. The lack of calories, caffeine and/or nicotine can cause significant physical and/or mental stress and may require early test termination. The latter is more likely with longer tests as there can be a higher risk of reactive hypoglycaemia. Finally, while the preparation period is important, in practice, most participants will exceed this carbohydrate intake, so the test can often be scheduled earlier than anticipated.

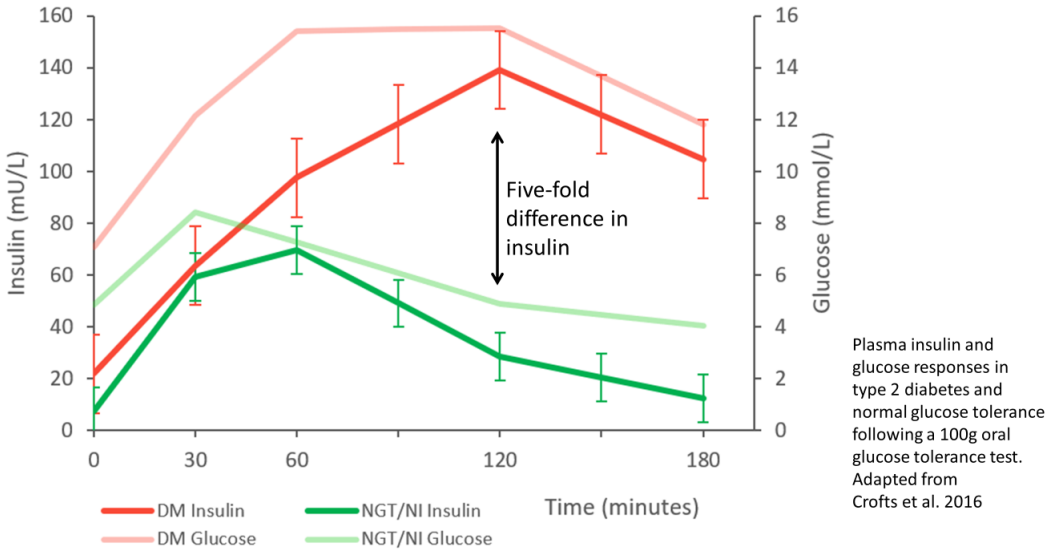


Figure 10: Kraft patterning in a healthy person compared to someone with T2D

Modified Kraft patterning

Given 'full' Kraft patterning is demanding, a modified version can be used, especially if the desired outcome is a simple dichotomy of "hyperinsulinaemic/insulin resistant" or not. For modified patterning, the same OGTT is performed but samples for insulin and glucose are only required at baseline and 120 minutes (25). BHB could be sampled at baseline, but a 120 min sample is unlikely to add further value.

While cheaper and easier for the person, less information is imparted, especially the presence or absence of the first phase insulin response. This may impair disease progression monitoring. Insulin peaking at 120 minutes or later has high predictability for development of T2D (26). This knowledge could influence the need for a more intense intervention.

Capillary proxy markers

While insulin is the most obvious metabolite for identifying hyperinsulinaemia it also poses significant challenges. While cost is readily apparent, what is not well recognised is that insulin is a very fragile protein that denatures easily, especially in the presence of haemolysis, leading to artificially low levels. Ideally there should be a very short period between sample collection and either freezing or analysis. These practical challenges mean that using a proxy marker may be sufficient for identifying hyperinsulinaemia.

The combination of glucose and BHB could be used as a proxy for insulin. The advantage to this is that, compared to insulin, both glucose and BHB are easily and cheaply sampled via either venous or capillary sampling. Capillary sampling is both less expensive and less invasive compared to venous samples and results can be returned in real-time. Furthermore, the technology for capillary sampling allows for testing to occur in primary care by a variety of health care professionals, or for self-testing. As a single sample, the demand and stress on the person is also significantly reduced.

This test only requires a fasting sample (minimum of two hours) that quantifies capillary glucose and BHB (often referred to as 'ketones'). A specialised meter and test strips are required, along with capillary blood sampling lancets. This equipment is readily available as it is considered standard for anyone with T1D.

Testing occurs either pre-breakfast, or ideally, pre-dinner (two hours after any food) although random sampling could be considered. Interpretation is based on the presence of normoglycaemia (3.5-6.0 mmol/L) and BHB > 0.3 mmol/L. However, interpretation can be further refined depending on knowledge of individual circumstances. For example, fasting glucose at the higher end of the range can indicate a greater cardiovascular risk (27), therefore, understanding the fasting period is important.

While pre-breakfast sampling may better indicate basal insulin secretion due to the longer fasting time, pre-dinner sampling may indicate metabolic response to the day's meals (the bolus response.

Inferring hyperinsulinaemia and/ or insulin resistance

As described above, insulin can be measured directly or indirectly to *quantify* hyperinsulinaemia. However, hyperinsulinaemia can also be *inferred* using clinical parameters. This means that testing may not be necessary in all circumstances unless baseline levels are considered appropriate for ongoing monitoring.

Table 3 proposes a model for when to quantify hyperinsulinaemia status in those 18 years of age or older[3] with three levels:

A. Insulin resistance / hyperinsulinaemia are recognised as a key component of clinical presentation. Until other clinical parameters improve, there is no additional value for quantifying hyperinsulinaemia.

B. Insulin resistance and/or hyperinsulinaemia are clinically, mechanistically and/or epidemiologically considered a key component of clinical presentation. Prodromal diabetes can be assumed to be a co-morbidity. Quantification may be beneficial to determine baseline condition to allow for monitoring.

C. High risk of developing prodromal diabetes. At least annual screening recommended.

Status A

Generally, in the absence of T1D or prolonged caloric/carbohydrate restriction, hyperglycaemia will not occur without concurrent hyperinsulinaemia and /or insulin resistance. Therefore, any condition that causes hyperglycaemia (HbA1c > 40 mmol/mol, fasting glucose > 6.0 mmol/L, postprandial glucose > 7.8mmol/L or random glucose > 11.1 mmol/L) can be considered co-morbid with hyperinsulinaemia and / or insulin resistance without further testing.

People with T1D are not immune to developing T2D (double diabetes). It is currently estimated that up to 50 units of insulin per day are secreted in a healthy person. Therefore, anyone with T1D using more than 60 units of insulin per day may be developing insulin resistance based on a higher than desirable daily usage.

Oral steroids are known to cause immediate insulin resistance and increase the risk of developing T2D. This risk has not been quantified against course length, but the longer the length, or frequently repeated courses would confer greater risk. Based on steroid tapering guidelines, “long-term” could be considered more than 21 days, or frequently repeated courses to the extent that dose tapering is required.

Other medications or conditions that are associated with a very high risk of future development of T2D include clozapine or olanzapine, a history of two or more pregnancies affected by gestational diabetes, polycystic ovarian syndrome (PCOS) and diabetic retinopathy while normoglycaemic.

Status B

Most conditions within status B are those with an aetiology that mechanistically include hyperinsulinaemia and/or insulin resistance, and/or have epidemiological associations with a moderate-high increased risk of developing T2D. However, as this group does not have an overt hyperglycaemia, their progression on the diabetes spectrum remains unknown. Kraft

[3] T2D is being increasing diagnosed in younger adults. This, and being the progeny of a person with pregnancy related issues may lead to children being referred for testing. However, this model is based on post-pubescent or ‘biological’ adults, therefore may not be generalisable to those under 17 years of age.

patterning may be beneficial to determine additional risk factors, such as the presence of first phase insulin response or rate of return of beta hydroxybutyrate.

Status C

Prodromal diabetes may last up to approximately 25 years before the development of hyperglycaemia, (12) and is believed to be predominantly asymptomatic. As this is proposed to be the optimal time to prevent the many metabolic conditions that have the common aetiology of hyperinsulinaemia and/or insulin resistance, screening will be necessary if results will impact intervention. When to start, and the frequency of, screening is yet to be determined, but should be personalised based on known risk factors. Hyperinsulinaemia screening should commence at sign of first risk factor, at least ten years before the age for diabetes screening, or after the age of 18 years, whichever occurs first. Based on current NZ guidelines, this means that hyperinsulinaemia screening would likely commence for all Māori, Pacific, or Indo-Asian men at 18-20 years. Using the proxy marker of glucose/BHB and testing in primary care facilities such as pharmacies, or setting up screening locations at sports venues, marae, churches, educational institutes or workplace settings may aid concordance.

Table 3: Model for testing or presuming hyperinsulinaemic status.

Status	Insulin resistance testing status	List of conditions
A	Insulin resistance confirmed. Confirming status not required.	• HbA1c > 40 mmol/mol[1] • Type 1 diabetes using ≥ 60 units insulin per day or using metformin • PCOS • History of ≥ 2 GDM pregnancies • Long-term use oral steroids • Long-term use clozapine or olanzapine • Diabetic retinopathy in the presence of normoglycaemia
B	Insulin resistance should be presumed until proven otherwise. Confirming status may be beneficial for intervention and/or monitoring.	• Primary hypertension[1] • Hypertriglyceridaemia[1] • Hyperuricaemia and/or gout[1] • Chronic subclinical metabolic acidosis and/or inflammation • History of pregnancy related issues – see Table 4 • First degree relative with T2D diagnosed before the age of 40 years. • Waist to height ratio > 0.5 • BMI > 35kg/m2 or >30kg/m2 if Indo-Asian (and not an athlete) [1] • Obstructive sleep apnoea needing CPAP • Post renal transplant • Long term antipsychotic treatment apart from clozapine • Chronic Hep C

C	Screening recommended	• Insulin resistance associated skin measures e.g.
		  ○ Acanthosis nigricans
		  ○ Skin tags
		• Taking long-term medication associated with insulin resistance
		  ○ Statins
		  ○ High dose niacin
		  ○ Combined oral contraceptives
		• History of pregnancy related issues – see Table 4
		• Progeny of people with pregnancy related issues
		• BMI 25-35kg/m2 or >23kg/m2 if Indo-Asian (and not an athlete)1
		• Rapid or concerning weight gain
		• 10 years before recommended age for diabetes screening
		• Unable to skip meals or gets ‘hangry’ if fasting for > 4 hours
		• Post organ transplant
		• Obstructive sleep apnoea

[1] and/or medications for these conditions

Table 4: Pregnancy related issues that confer a greater risk of T2D in either the parent or offspring.

Pregnancy related issues	
Status B	Status C
Gestational diabetes mellitus (GDM) Severe preeclampsia Gestational hypertension	Mild – moderate pre-eclampsia Macrosomia Small for gestational age, or low birth weight babies Significant weight gain during pregnancy

Management

Generally, the objectives of any medical or health-improvement intervention is to provide a cure, mitigate effects, induce disease reversal or remission, or prevent a disease state from occurring in the first place. These methods may include lifestyle, pharmacological, surgical, and/or psychological management strategies. Typically, medical interventions (including pharmacological and surgical interventions) occur following a formal diagnosis. Prior to that, the person must self-manage although may receive support and self-management resources from their health-care providers.

With respect to conditions on the T2D spectrum, "prediabetes" is currently the point where medical intervention, including education specific to T2D could typically be expected. Although this approach does reduce the risk of 'over-medicalising' people on the diabetes spectrum, it also means that the optimal point for intervention (i.e. prodromal diabetes) is missed. Based on inferences from current research and clinical programs, no person with prediabetes or T2D has ever fully reversed their insulin resistance status despite long-term remission of their hyperinsulinaemia.

Therefore, society needs to implement effective interventions for people in prodromal T2D, to see if a cure can be implemented, rather than the current best standard of remission.

As prodromal diabetes is not recognised as a medical condition, there are currently no pharmacological or surgical management strategies indicated for treatment. Lifestyle and cognitive strategies that address hyperinsulinaemia are recommended. Successful management of hyperinsulinaemia will therefore address other conditions that are aggravated by high insulin levels. Therefore, management will focus on lifestyle and cognitive therapies with mechanistic and/or proven basis in practice.

Lifestyle overview

The first step to restoring health is to ensure metabolic flexibility. Until the person can successfully burn fat, weight-loss strategies will be unsustainable and improving cardiorespiratory fitness will also be difficult. Lifestyle change is the only known strategy, especially from movement (physical activity), eating patterns, stress management and sleep

(MESS). Other measures such as addressing smoking/vaping or excessive alcohol consumption should always be considered given their wider health benefits. There are many other measures that should also be considered to optimise metabolic health outcomes, including supplements, sunlight exposure, reducing pollutant exposure, time spent in green/blue spaces, and social/spiritual connections. While the impact of these latter measures has less impact on addressing hyperinsulinaemia compared to the MESS changes, their overall impact to general health should not be underestimated.

The four key components to lifestyle modification are intertwined and each will influence the others. While dietary modification is hypothesised to account for 80% of improvements to hyperinsulinaemia, improving movement, sleep and stress are no less important. In fact, improving sleep and/or stress levels may need to be addressed before changes to eating patterns or movement can be successful.

This is why lifestyle changes must be personalised for greatest impact. There are many factors that can influence the success of any given program or recommendations and may include age, or life stage, culture, current health needs, and many different socioeconomic influences, especially money or time availability. Having descriptive programs which allow for strategy personalisation may allow many people to reach the same end goal (i.e. normalised insulin levels) via different methods. However, while some people can derive their own program from guidelines for effective results, many cannot and will require additional psychological support.

Measuring change

It can be difficult to quantify change to metabolic health, especially when symptoms are mostly invisible and may be confounded by other changes (e.g. gaining muscle while losing fat may create a net balance while using scales or clothing sizes as the assessment tool). Some people create detectable changes quickly, while others may be discouraged by a slow rate of visible progress. This is why precise data collection is important. Blood measures, especially glucose and beta hydroxybutyrate, can detect change quickly and precisely so should be used as the foundational measure of change. Maintaining euglycaemia while sustaining BHB is the easiest way of assessing metabolic flexibility. BHB > 0.3 mmol/L and glucose 3.5-5.0 mmol/L at least 2-hours postprandially are considered a proxy for well-controlled insulin levels and the restoration of lipolysis and ketogenesis. Maintaining these levels should be a baseline goal for everyone.

Glucose/BHB levels can be assessed with a single capillary sample. Initially, this should be at least daily until new habits are entrenched, then frequency decreased to whatever maintenance frequency is deemed appropriate. This can be problematic for many people as many are needle phobic and adherence to monitoring decreases with sore fingers. Continuous monitoring may be preferred, especially in the early phases of behaviour change, as only one skin puncture is required for 14 days of monitoring.

Continuous monitors

Continuous glucose monitors have been available for years, while continuous ketone monitors are an emerging technology. The monitor system includes a small sensor that is inserted just under the skin, usually on the upper, outer arm and measures glucose/BHB levels in the interstitial fluid (close correlation to capillary levels). Data is wirelessly transmitted to the person's phone or reader to be displayed in different ways for analysis.

The data can often also be transmitted to the healthcare provider for overview, but also to help interpreting trends for both the individual and on a population basis.

CGMs are widely used for people with T1D or those prescribed insulin therapy as they provide early warnings for hypo-or hyperglycaemia. However, the measure of "time in range (TIR)" is emerging as being more effective to predicting long-term health outcomes. The current widely used measure of glycaemia control is HbA1c, which estimates the means glycaemic control over the previous 12 weeks. However, as it is an average, the same result may occur for someone who has maintains steady glycaemic control as well as someone who has vastly variable control, but whose 'highs' are balanced by the 'lows'. Variable control is associated with poorer health outcomes but cannot be assessed by HbA1c alone. Using CGMs and TIR both assesses risk of poor health outcomes, but also indicate in *real-time* when these moments occur, which may affect long-term behaviour change.

There is limited research on use of CGMs in people with prodromal diabetes, or for influencing long-term sustained behaviour change, despite increasing use for this purpose. A small clinical program in rural New Zealand showed that 2-4 weeks of CGM use improved HbA1c in some people by approximately 10 mmol/mol over three months when supported by education and advice (Personal communication). Although this project was interrupted through Covid and lack of ongoing financial support, it demonstrates the potential value of the technology, as 10 mmol/mol is generally considered an effective intervention for diabetes and three months is a relatively short-time phase. It remains unknown what factors within that project were key to success, i.e. was it the CGM providing real-time feedback on lifestyle choices and/or the education and support provided.

Given the relatively low cost of the CGM/CKM monitors (~$100 for two weeks), their use should still be considered as part of any metabolic health intervention despite the lack of formal research.

Eating patterns

Any eating pattern that normalises insulin levels while ensuring adequate intake of protein, calories, and naturally sourced micronutrients, which also minimises ultra-processed food consumption should be considered. This allows personalisation for cultural and other preferences. While there is considerable research about many different eating patterns and how each can improve health, it is often not discussed how each approach can worsen the health of a small group of individuals – hence the need for personalisation. Therefore, individual strategies will not be discussed. It is worth noting though that significant success occurs when:

1) Total carbohydrate intake is reduced, especially that derived from simple sugars (e.g. low glycaemic load)
2) Ultra-processed food consumption is minimised
3) A wide variety of foods are consumed
4) Snacking (between meal eating) is minimised
5) Fermented foods are included for gut health (e.g. microbiota, intestinal permeability)
6) Protein and micronutrients are prioritised
7) Vintage fats are prioritised over highly refined oils with a high omega-6 content

Movement

The principles surrounding optimal physical activity can be summarised in Figure 11. Non-exercise Activity Thermogenesis (NEAT) is energy expended not from planned exercise (e.g.

sports or gym), sleeping or eating, and may include activities such as housework, gardening, or active modes of travel (e.g. walking to work) (28). Physical activity is well recognised to have health benefits beyond physical/metabolic health as it is recognised to improve overall mental wellbeing, showing an interconnected effect on both reducing stress and sleep (29).

Activity conducted in 'green' or beside 'blue' spaces (e.g. parks or beside waterways) have been shown to confer additional mental health benefits (30). This may relate to decreased stress or pollution exposure and/or greater social or spiritual connections (31).

There are many different options for increasing physical activity, from increasing planned exercise (e.g. team or individual sports, gym membership, community events) to increasing NEAT. However, like eating patterns, physical activity should also be personalised. Measuring change may be easier with the use of technology such as fitness trackers and phone apps.

Figure 11: Principles of physical activity

Unfortunately, movement must be assessed carefully as it can be easy to be overzealous and cause harm, rather than benefit. For example, increased physical activity needs to cause some physical stress as the repair processes cause increased strength and endurance adaptations. However, inflammation caused by excessive exercise with insufficient recovery can increase cortisol and lactate, which can have the follow-on effect of increasing insulin. Excessive physical activity or incorrect technique and/or equipment may also result in injuries, which can impede progress as well as increasing cortisol and/or lactate, thus increasing insulin.

Sleep

It is well recognised that sleep is critical to all aspects of health, but especially metabolic health. Both quantity and quality of sleep architecture contribute uniquely to various aspects of health. In a healthy sleep cycle, individuals transition from lighter non-REM (rapid eye movement) stages (Stages 1 and 2) to the deeper stages (Stages 3 and 4), with the deeper

stages known collectively as slow-wave sleep (SWS). This is followed by a period of REM sleep. A complete sleep cycle will last 90-120 minutes and will be repeated throughout the sleep period.

SWS is widely acknowledged as the most rejuvenating phase of sleep and is primarily associated with essential physiological restoration, including the regulation of endocrine and autonomic variables. Of note, glymphatic drainage, the brain's waste removal process, occurs during SWS. Glymphatic drainage literally 'washes' the brain thus facilitating the clearance of toxins and metabolic byproducts (32). By contrast, REM sleep supports cognitive restoration including memory consolidation, emotional regulation, creativity, and neurotransmitter balance (33).

However, if sleep is disturbed, generally a new sleep cycle is commenced, meaning SWS and REM sleep are most likely to be truncated. Furthermore, SWS typically has longer periods in the earlier part of the night compared to REM, but as sleep progresses, SWS shortens and REM periods lengthen. This means that delays with sleep onset, or early awakenings will further truncate SWS and/or REM sleep.

Deficits in either SWS or REM are associated with metabolic disfunction due to a variety of factors, including increased hypothalamic-pituitary-adrenal (HPA) axis activation or increased emotional dysregulation the following day. Both lead to increased noradrenaline and cortisol, which increases insulin resistance.

Metabolic inflexibility further disrupts sleep, as an inability to burn fat causes appetite dysregulation and the need to consume carbohydrates every 4-6 hours. This means that people often eat late or wake early due to hunger, further disrupting natural circadian rhythms and sleep architecture.

Stress

Optimal health requires stress exposure followed by adequate recovery (eustress). The stress exposure, e.g. moderate physical activity, or learning a complex process within a short timeframe, causes 'microtraumas', triggering a variety of growth and repair processes. When balanced with adequate recovery and healing, the stress allows growth, thus fortifying the body against more severe stressors. As previously described, stress increases insulin resistance and insulin secretion. In an appropriate dose-response, the insulin is beneficial as it promotes repair processes, thus healing. However, if the stress is sustained, repair and recovery is prevented, resulting in greater secretion of cortisol, insulin resistance, and hyperinsulinaemia. Stress also increases appetite in most people, who then tend to eat more sweet foods (34), thus perpetuating the cycles.

Making and sustaining change

For sustained health benefits, change should be, at minimum, co-designed by tangata whaiora, be based on objective and personalised data, be implemented collectively, and become integrated in the physical, cultural, and social environments (Figure 12).

Figure 12: The 6P model for lifestyle program design (35)

However, a precise strategy involves the collection and analysis of individual data, that then must be interpreted against the underlying science, then re-applied against an individual to produce a personalised strategy. Most people lack sufficient knowledge or skills to achieve this in all MESS domains. Many people will seek support in individual domains, such as working with a nutritionist or a personal trainer. However, these specialists may not have sufficient knowledge in the other domains or may only provide short-term interventions.

It is well recognised that long-term behaviour change is difficult without sufficient psychological support. Health coaches are an emerging group of healthcare professionals who can provide that psychological support. A health coach 'walks alongside' individuals to help guide and support them in making positive lifestyle changes to achieve their health and wellness goals. Generally, health coaches have foundational knowledge to support all MESS domains but may have specialist knowledge in one or more domains. More importantly, health coaches empower tāngata whaiora to take ownership of their health journey, from setting goals, to identifying and resolving barriers. This means the tangata whaiora becomes an active participant in their own recovery, so are more likely to make sustainable change.

Health coaches are becoming an integral part of intradisciplinary health teams, especially in preventative health care and/or lifestyle management of chronic health conditions where they may be the primary contact. They can refer tāngata whaiora to more specialised assistance as required, such as a nutritionist or fitness instructor, while supporting the specialist advice over a longer period. This collaborative approach allows health coaches to provide comprehensive psychological support for as long as required. This ensures tangata whaiora receive appropriate guidance and resources for their unique needs. Working this way, health coaches help drive all aspects of the 6P model suggested for lifestyle program design.

Sustained change cannot happen in a vacuum. Tangata whaiora need support from increasingly wider circles, from whānau, employers, social circles, but also wider social constructs and norms. The physical and cultural environment likely has a larger role in behavioural change then currently realised. Understanding the wider impact of insulin on health is an important part of the process, followed by 6P implementation.

Kia manaaki tātou I ngā tamariki, ngā kōtiro, me ngā tama,
kia whakatupui te whaiao āpōpō
(Let us support and care for the children, the girls, and the boys, to cultivate the world of tomorrow).

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