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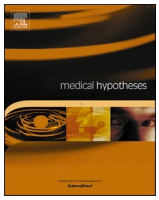

Glycation of Myoglobin: A positive feedback loop reinforcing insulin resistance

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ABSTRACT

Prevailing theory ascribes insulin resistance to improper cellular responses to insulin. However, insulin's effectiveness as a control mechanism depends not just on the uptake of glucose into tissues, but also its utilization once there and so, impaired cellular responsiveness to glucose itself could be a cause, or feature, of insulin resistance. Glucose utilization, in turn, depends on oxygen availability and so, obstructed cellular oxygen delivery, if present, could plausibly contribute to insulin resistance. This paper presents the hypothesis that glycated myoglobin in muscle tissue, resulting from persistent hyperglycemia, could impair oxygen availability and thereby reduce cellular responsiveness to glucose. It is further hypothesized that this creates a positive feedback loop where hyperglycemia is exacerbated by glycation resulting from hyperglycemia. The presence of a positive feedback loop is consistent with the progressive nature of metabolic syndrome and Type 2 Diabetes, and also with their recalcitrance to treatment. It is therefore proposed that glycation of myoglobin is a contributing mechanism in disease progression in these conditions, and that its measurement could serve as both a long-term marker of progression and as a predictor of future risk.

Introduction

Insulin resistance refers to a system-wide reduction in cellular responsiveness to insulin, which impairs the ability to dispose of blood glucose through cellular respiration [1]. The prevailing understanding is that this resistance arises due to cellular unresponsiveness to insulin. There are a number of established mechanisms by which insulin resistance develops. Lee et al. (2021) provide a comprehensive review of these pathways, highlighting the multifactorial nature of insulin resistance [2]. One such mechanism involves disruption of the insulin signalling cascade via the hexosamine biosynthesis pathway (HBP), wherein protein O-GlcNAcylation modifies key components of the insulin pathway, thereby impairing glucose transport [3]. Additionally, hepatic insulin resistance—commonly observed in obese and type 2 diabetic individuals—has been associated with the excessive accumulation of hepatic diacylglycerol (DAG), which activates protein kinase C isoforms. This activation interferes with insulin receptor function and downstream signalling, contributing to metabolic dysregulation [4,5].

The above mechanisms describe scenarios where insulin receptor is decreased, impairing the transfer of sugar from blood to tissue, thereby reducing insulin's effectiveness in its role of modulating blood sugar levels. Models of that sort cannot be a complete description of insulin resistance, however. Obstructed passage of sugar into tissue as a sole mechanism for insulin resistance is not consistent with the observations that individuals with insulin resistance tend to also display symptoms of excess sugar in tissue, such as the glycation of myoglobin in skeletal muscle tissue[6]. Consequently, it can be inferred as likely that other mechanisms act to impair the utilization of sugar once it is in the tissue.

One such mechanism is mitochondrial dysfunction, which is often induced by chronic nutrient excess and further contributes to insulin resistance through impaired oxidative metabolism, increased ROS production, and altered mitochondrial dynamics, including enhanced fission and reduced fusion [7]. Mechanisms that render insulin ineffective at transporting glucose into tissues and mechanisms or impair cellular responsiveness to glucose itself offer a fairly broad description of insulin resistance, but this description omits the role of the other critical reactant involved in respiration: Oxygen.

According to Le Chatelier's principle of reaction kinetics, an increase in glucose concentration within a tissue should, in theory, enhance the rate of glucose metabolism. However, this expected first-order kinetic response would be diminished if oxygen became limiting. Consequently, tissues that experience oxygen deficiency would be unsuitable for

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glucose-driven respiration, as oxidative phosphorylation would be impaired.

In an acute hyperglycemic state, a negative feedback loop is initiated wherein insulin facilitates glucose uptake into tissues [8]. In healthy muscle tissue, where oxygen is readily available, the increased intracellular glucose concentrations drive higher respiration rates, promoting energy production [9]. However, in cases of chronic hyperglycemia, a positive feedback loop may emerge. Persistently elevated blood glucose levels can lead to non-enzymatic glycation of proteins, resulting in structural and functional impairments in cellular components [6]. This glycation process impairs oxygen delivery and therefore compromises the ability of muscle tissue to respond effectively to glucose, ultimately exacerbating insulin resistance and metabolic dysfunction.

In healthy muscle tissue, myoglobin serves a crucial role as both a shuttle and reservoir for oxygen [10]. With a higher affinity for oxygen than hemoglobin, myoglobin extracts oxygen from the blood and facilitates its transport into muscle cells, ensuring a steady supply for aerobic respiration and a readily-available reserve under anoxic conditions [10]. The oxygen tension gradient further drives the movement of oxygen from myoglobin to muscle cells, particularly during periods of increased demand, such as exercise.

If myoglobin undergoes degradation, including due to glycation, its ability to transport and store oxygen becomes compromised. Mechanistically, this degradation would lead to chronic under-oxygenation of muscle tissue, especially during states of increased oxygen demand [11]. The resulting oxygen deficiency would not only impair oxidative metabolism but also affect the overall reaction kinetics of glucose metabolism. In muscle tissue with glycated myoglobin, the expected metabolic response to elevated glucose concentrations would be diminished due to impaired oxygen availability, further exacerbating metabolic inefficiencies in insulin-resistant states.

Hypothesis

The hypothesis is that conditions of chronic insulin resistance are characterized by a positive feedback loop of glycated myoglobin impairing glucose disposal, exacerbating hyperglycemia. It is further proposed that levels of glycated myoglobin in muscle tissue may be used as a predictor of future risk of metabolic syndrome and as a marker of disease progression. A causal loop diagram illustrating the hypothesized positive feedback loop is shown in Fig. 1.

It is further hypothesized that the pro-inflammatory and autoimmune stimulus resulting from glycated myoglobin contribute to other signs and symptoms associated with metabolic syndrome and reinforce the hypothesized positive feedback by disrupting endothelial function and thereby impeding oxygen transfer into tissue [6]. In this proposed mechanism, glycation of myoglobin would be considered an active cause of insulin resistance rather than just a long-term symptom of it.

An extension of the hypothesis is that measurements of glycated myoglobin will be reflective of existing disease progression and predictive of future disease progression. While a relatively uncommon procedure, levels of myoglobin in muscle tissue have been known to be measured using a needle biopsy from the quadriceps muscle under local anaesthetic. Radioimmunoassay can further be used to determine levels of non-glycated and glycated myoglobin. [8,12].

Evolution of the hypothesis

The formation of Advanced Glycation Endproducts (AGEs) is known to be encouraged under conditions of hyperglycemia, and accumulation of AGEs has been associated with a number of pathological conditions [13]. Consequently, glycation can be considered a disease process associated with hyperglycemia in general, and in particular with the persistent hyperglycemic conditions associated with insulin resistance.

Since AGEs are formed by the conversion of biologically-functional proteins, the biological functions of those proteins tend to be disrupted by their formation, and their presence tends to lead to, or contribute to, pathophysiological events [13]. If the formation of AGEs through some mechanism disrupts the proper disposal of blood sugars the expected result would be a positive feedback loop in which by-products of hyperglycemia exacerbate the underlying conditions leading to that hyperglycemia. Positive feedback loops tend to result in progressive illness, and metabolic syndrome, pre-diabetes and Type 2 diabetes are well-known to be progressive in nature, tending to worsen over time once they have developed initially [14].

It has been determined that insulin resistance in skeletal muscle tissue, specifically, is the most significant contributor to dysfunctional glucose metabolism in Type 2 Diabetes [15]. Hence, there is good reason to consider the possibility of AGEs that form in muscle tissue as likely candidates for disruption of glucose utilization and contributing causes

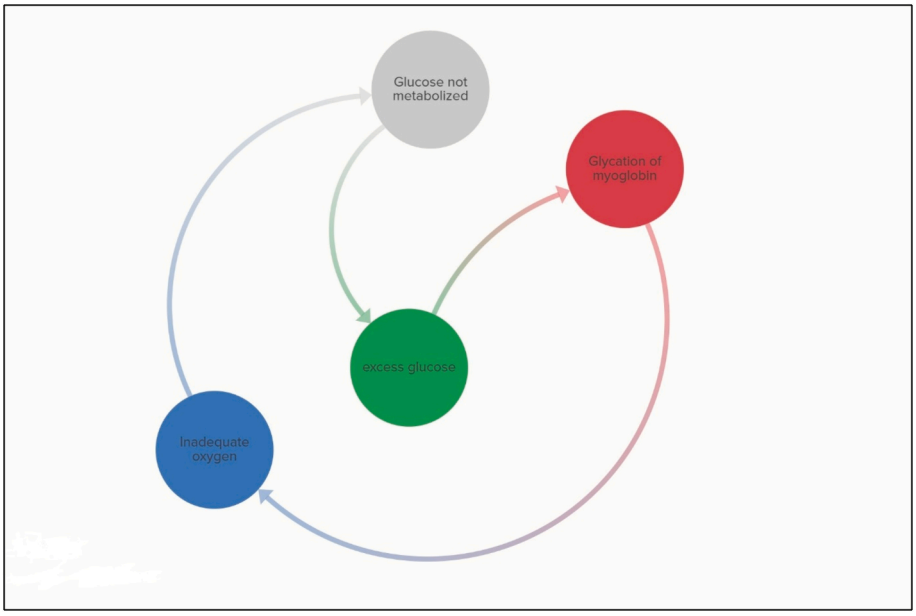

Fig. 1. Causal loop diagram illustrating a positive feedback loop where excess glucose arises from impaired oxygen delivery, resulting in glycation and further impairing oxygen availability.

of disease progression in conditions characterized by hyperglycemia.

A likely candidate for this would be myoglobin, a heme protein present in muscle tissue, the primary functions of which are to act as an intermediate compartment facilitating the transfer of oxygen from blood into muscle cells and to serve as a reservoir of oxygen to support oxidative phosphorylation during bouts of high oxygen demand or limited oxygen availability. According to some sources, myoglobin storage accounts for around 200 ml of oxygen while dissolved oxygen in tissue fluids accounts for just 45 ml, although estimates of these values vary between sources [16]. This means that myoglobin represents a significant oxygen reservoir and it would follow that disruption of oxygen transfer to and from that reservoir, or disruption of its storage capacity, would therefore disrupt oxygen storage and usage dynamics in tissue broadly but particularly in skeletal muscle, the most metabolically active tissue type and the one that most strongly contributes to the state of insulin resistance [11].

The intuitive expectation is that if myoglobin becomes degraded, thereby impairing the majority of the body's tissue-based oxygen storage, oxygen dynamics would be commensurately affected. The absence of a reservoir that buffers oxygen levels would naturally be expected to result in oxygen insufficiency in periods of high demand, and also excess oxygen when it is abundant without a reservoir to absorb that surplus.

There are other observed characteristics of insulin resistance related conditions which are consistent with system behaviour that would be expected if the hypothesis is correct. Firstly, hyperlactatemia frequently presents in Type 2 diabetics [17]. Lactate production in skeletal muscle is a direct result of inadequate oxygen supply and so, over-production of lactate would be an expected observation under conditions of chronically impaired oxygen delivery.

Secondly, it has been found that the progression of glycation affects the rate of proteolysis, the breakdown of myoglobin. For moderately glycated myoglobin, proteolysis is accelerated but for highly glycated myoglobin, proteolysis becomes impaired [18]. This phenomenon would be expected to result in threshold behaviour where acute hyperglycemia is self-correcting but becomes recalcitrant if it progresses to a stage where myoglobin is sufficiently glycated for proteolysis to become impaired.

It has also emerged that insulin resistance presents in Type 1 Diabetes, a disease condition characterized by the absence of endogenous insulin, requiring the administration of exogenous insulin in closely monitored and regulated doses, but also typically characterized by the presence of chronic hyperglycemia [19]. The development of insulin resistance under such conditions is consistent with a contributing mechanism for insulin resistance that results from over-exposure to glucose rather than to insulin.

The hypothesis is also consistent with experimental findings that creatine monohydrate improves blood sugar management in Type 2 Diabetics [20]. Creatine supplementation results in larger muscle stores of Adenosine Triphosphate (ATP), which effectively serves as an alternative oxygen store by yielding energy without oxygen consumption [21].

There is evidence that excessive myoglobin glycation also has immunogenic and pro-inflammatory effects and the increased production of AGEs associated with diabetes is commonly reported as a central cause of diabetic microvascular and macrovascular complications [6]. This observation is consistent with the proposed hypothesis, as it links the progression of metabolic disease to the glycation of myoglobin, making myoglobin central to the progression of insulin resistance and its adverse health effects.

The hypothesis is also consistent with the observation that Type 2 Diabetes results in an excess of Reactive Oxidating Species (ROS). Tang et al [6] describe one of the roles of myoglobin as that of 'quenching' ROS, and elaborates further that glycation impairs this function.

In summary, the hypothesis is mechanistically plausible and is consistent with a number of real-world observations which are otherwise not well understood or poorly described by current models.

Implications of hypothesis

If this hypothesis is correct and glycated myoglobin is a contributing cause underlying conditions of insulin resistance, it would have widespread implications for the future prospects for diagnosis and management of these conditions, as well as our fundamental understanding of their mechanisms of progression. It would imply that the degree of glycation of myoglobin would be highly accurate as a diagnostic criterion and predictive tool for conditions of insulin resistance. The degree of glycation in hemoglobin is currently used as a marker of the cumulative effects of hyperglycemia over time and is considered to be more representative of a patient's glycemic state than instantaneous measures of blood sugar [22]. However, glycated hemoglobin is an effect of hyperglycemia and not a contributing cause of it and so, while it will accurately reflect past glycemic trends, it is not necessarily predictive because it doesn't have a direct causative link to future sugar levels. If the present hypothesis is correct, however, and glycated myoglobin is directly causative of insulin resistance, then measurements of it as a marker should be more predictive of future blood sugar stability.

This would suggest that assays of glycation levels in myoglobin would offer an accurate tool for early detection of insulin resistance, offering an opportunity for targeted intervention before disease progresses to the positive feedback loop hypothesized in this paper. During this window where myoglobin is moderately glycated and proteolysis is accelerated rather than inhibited, it would be expected that lifestyle modifications would still be effective at reversing disease progression whereas during the subsequent stages, when glycation is advanced and proteolysis is inhibited, effective treatment may require more extreme interventions [18].

According to an extensive review by [23], analytical methods for measuring the extent of glycation in myoglobin are an emerging science, not yet well-developed for clinical applications but rapidly advancing. That review further states that a number of the current methods do not directly measure glycation but instead test for biomarkers in the blood. This is promising for clinical applications related to the present hypothesis, because it allows for non-invasive measurement. The same review also states that there are emerging *trans*-cutaneous methods of measurement using fluorescence, but that these methods are limited to detection of those specific AGEs that are fluorescent, and that no single test identifies all markers of glycation. It is also reported that Near-Infrared Spectroscopy (NIRS) can detect AGEs transcutaneously [24]. However, the authors of [23] state that the correlation between biomarkers and actual extents of glycation do not correlate perfectly, and another review reports that circulating levels of AGEs can be affected by exogenous sources[25].

Hence, while non-invasive methods currently exist, and could be clinically useful for the present hypothesis, the standard means for determining the extent of glycation currently depend upon muscle biopsy and subsequent analysis using either microscopy or Western blot techniques[26]. The muscle biopsy required for assay is an invasive and uncomfortable procedure, and therefore not possible to conduct on a high-frequency basis. Hence, its role, if the hypothesis is valid, would be primarily as an infrequent measure of disease progression, not a tool for daily monitoring and control. It is also not yet clear which muscle would be ideal for sampling, or whether perhaps biopsies from multiple sites would be required to achieve a representative sample, exacerbating the problem of invasiveness. Consequently, clinical monitoring would most likely entail an initial biopsy to determine the current state of glycation, with ongoing monitoring relying on tracking the progression of blood-borne biomarkers coupled with fluorescence testing, with biopsies conducted only infrequently for evaluating long-term disease progression. The rapid development of new non-invasive methods for measuring AGEs is a promising indicator that over time, it will become possible to determine the extent of glycation with increasing ease and accuracy which means that the present hypothesis, if confirmed, will gain additional clinical utility as measurement techniques improve.

Under the present hypothesis, glycated myoglobin would also present a promising therapeutic target for addressing recalcitrant insulin resistance. Removing any one of the causal steps shown in Figure One would break the cycle of the positive feedback loop, and allow remediation of the normal metabolism of blood glucose. One avenue of particular interest would be that of administering drugs that promote proteolysis of glycated myoglobin, which would speed up the turnover of otherwise long-lived degraded myoglobin, offering a means of exiting the positive feedback loop hypothesized in this paper [18]. Aside from the glycated myoglobin itself, this hypothesis suggests another therapeutic target, namely the chronic undersupply of oxygen in skeletal muscle. The use of creatine monohydrate to treat Type 2 Diabetes is consistent with this therapeutic target, but other interventions suggest themselves, such as exercise under hyperoxic conditions to deliver oxygen to skeletal muscle, or intermittent hypoxic training as a means of increasing the body's native capacity to deliver oxygen. A study examining the effects of induced hypoxia on myoglobin expression found that while hypoxia in isolation did not increase myoglobin gene expression, the combination of exercise and hypoxia was effective in inducing adaptive responses upregulating myoglobin production[27]. This suggests intermittent hypoxic training with concurrent exercise as a promising avenue for accelerating myoglobin turnover, replacing glycated myoglobin and remedying the hypothesized feedback loop.

Glutathione has been found to mitigate or reverse the effects of glycation [28], and a number of naturally-occurring compounds have been identified with properties that inhibit glycation [25]. Subsequent research efforts could study exercise and diet regimes in terms of their effect on myoglobin stores, and thereby identify non-pharmaceutical interventions well-suited to interrupting the emergence of the positive feedback loop proposed in this paper, as well as pharmaceutical interventions addressing glycation as a therapeutic target.

Testing of hypothesis

The first and most critical step in testing this hypothesis would be assaying the degree of glycation in myoglobin in a large cohort of patients with advanced conditions of insulin resistance, particularly Type 2 Diabetes. This would present an opportunity for initial falsification of the hypothesis; if glycated myoglobin is not present in a majority of those patients then the hypothesis, as formulated, would be demonstrated as untrue.

If the hypothesis were to survive that first stage of falsification and it transpires that the majority of Type 2 Diabetics present with glycated myoglobin, the next stage of testing would entail determining the degree of correlation between the extent of glycation and the severity of diabetic symptoms. Of particular interest would be confirming whether glycation is specifically correlated with symptoms associated with anoxic conditions, primarily hyperlactatemia.

Confirmation of the hypothesis would then require the recruitment of a cohort of pre-diabetic patients and the measurement of their degree of glycation along with other conventional markers of disease progression. If the hypothesis is correct then it would be expected that degree of glycation at intake would correlate strongly with development of Type 2 Diabetes during long-term follow-up. In particular, that correlation would be expected to be closer than that of the other markers.

The above clinical approach would evaluate the predictive power of glycated myoglobin in predicting subsequent disease progression, but would not necessarily unpack the causative mechanisms and hence, more targeted study would be needed to isolate specific factors. In vitro study using cultured skeletal muscle cells could give some insight into the mechanisms and rate of glycation in the presence of glucose and, perhaps more importantly, determine whether glycated myoglobin directly interferes with cellular oxygen metabolism and signalling. However, the hypothesis deals with the dynamic interactions of an interconnected system and so, isolated cellular study wouldn't be entirely instructive in unpacking overall behaviour.

Hence, animal models such as diabetic mouse models may be needed to provide reliable data with a high sample size. Alternatively, hyperglycemic clamp studies could be conducted on human subjects who have had measurements of myoglobin glycation to quantitatively measure the correlation between glycation degree and blood sugar disposal.

Conclusions

There is a strong mechanistic argument in favour of the hypothesis that glycation of myoglobin is a contributing cause of insulin resistance. The hypothesis is also consistent with a number of real-world observations that are otherwise poorly explained, and there is a considerable body of correlative evidence of the specific behaviours implied by this specific mechanism.

However, experimental evidence sufficient to either confirm or deny the hypothesis is not available. Such evidence would have to consist of clinical trials measuring glycation of myoglobin at different stages of metabolic illness, with long-term follow-ups to assess its predictive power as a diagnostic criterion. In vitro studies of cultured cells, animal models, and hyperglemic clamp experiments with human subjects could all provide insights into the specific mechanisms involved.

If subsequently confirmed, the hypothesis would offer a powerful diagnostic tool for metabolic illness, allowing for an occasional muscle biopsy to offer a clear picture of the degree of disease progression, predictive of future behaviour.

The concept introduced in this paper also presents a set of therapeutic targets allowing for better treatment of conditions of insulin resistance. If it transpires that the disruption of muscle oxygen reservoirs by glycation is in fact a significant contributing factor in insulin resistance, that would imply that any treatment options enhancing oxygen availability in muscle tissue would improve blood sugar management in metabolic syndrome and Type 2 Diabetes. Even if the hypothesis is not borne out, the general principle that oxygen availability will contribute to the rate of glucose utilization implies that interventions aimed at improving perfusion and oxygen availability merit trials for their efficacy in improving blood sugar management.

Ethics statement

This manuscript did not involve any human or animal subjects, and hence no consent was required. Research was conducted within the ethical guidelines prescribed by the University of the Witwatersrand.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process (must go before references)

Early stages of drafting this manuscript utilized ChatGPT to improve readability and clarity. Subsequent drafts extensively edited and rewrote this material and the authors take full responsibility for the content of the manuscript as submitted.

CRediT authorship contribution statement

Neil T. Stacey: Conceptualization, Writing – original draft. **Zoë da Silva:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation. **Nidal Boorany:** Resources, Investigation. **Joseph O. Palos:** Writing – review & editing. **Cole Potgieter:** Writing – review & editing. **Luke W. Pieterse:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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