

# MODERATE HYPOXIA EXPOSURE: A NOVEL STRATEGY TO IMPROVE GLUCOSE METABOLISM IN HUMANS?

Max Vogel, Ellen Blaak, \*Gijs Goossens

Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, Netherlands

\*Correspondence to G.Goossens@maastrichtuniversity.nl

**Disclosure:** The authors have declared no conflicts of interest.

**Received:** 22.07.15 **Accepted:** 03.09.15

**Citation:** EMJ Diabet. 2015;3[1]:73-79.

## ABSTRACT

The obesity epidemic calls for novel strategies to prevent and treat obesity and its comorbidities. Several studies have indicated that the amount of oxygen to which tissues are exposed may substantially impact cardiometabolic health. Interestingly, living at high altitude (hypobaric hypoxia) seems to be associated with improved glucose homeostasis and a decreased prevalence of Type 2 diabetes. Furthermore, normobaric hypoxia exposure has been shown to exert beneficial effects on glucose homeostasis and insulin sensitivity in rodents and humans. This may, at least in part, be explained by altered adipose tissue and skeletal muscle oxygen tension. In contrast, patients with obstructive sleep apnoea syndrome, which is characterised by episodes of severe intermittent hypoxia due to periodic collapse of the upper airway during sleep, show impairments in glucose homeostasis and are at increased cardiovascular risk. These discrepancies may be explained by the severity, duration, and pattern (number of cycles) of hypoxic episodes, but underlying mechanisms have not yet been studied in detail. The purpose of this review is to provide an overview of available studies on the link between oxygen tension, inflammation, and glucose homeostasis. Detailed studies to elucidate the effects of moderate hypoxia exposure on whole-body and tissue-specific insulin sensitivity in humans are clearly warranted.

**Keywords:** Oxygen tension, obesity, adipose tissue, skeletal muscle, insulin sensitivity, glucose metabolism.

## INTRODUCTION

The current obesity epidemic is accompanied by an increased prevalence of Type 2 diabetes (T2D)<sup>1</sup> and cardiovascular disease (CVD).<sup>2</sup> Insulin resistance, which may be present in multiple metabolic organs such as adipose tissue, skeletal muscle, and the liver, is one of the key processes in the development of T2D. Weight gain during the development of obesity is accompanied by adipose tissue dysfunction, which in turn contributes to excessive lipid accumulation in non-adipose tissues (ectopic fat deposition) when fat oxidative capacity is insufficient.<sup>3,4</sup> It has been known for many years that an impaired function of adipose tissue and skeletal muscle is strongly related to peripheral insulin resistance and T2D.<sup>5</sup> Lifestyle interventions have been shown to be effective in the prevention of T2D and cardiometabolic complications,<sup>6,7</sup> but there is large

variability in the response to these interventions. This creates the need for additional strategies to improve cardiometabolic health in individuals at increased risk of developing CVD and T2D. Interestingly, there is evidence to suggest that modulation of oxygen availability may be a novel therapeutic avenue to prevent and treat cardiometabolic diseases, as will be discussed in more detail below.

## LIVING AT HIGH ALTITUDE, AMBIENT OXYGEN TENSION, AND GLUCOSE HOMEOSTASIS

Epidemiological data on the effects of living at high altitude on mortality from chronic diseases are somewhat conflicting, in part due to differences in ethnicity, behavioural factors, and complex interactions with the environment. Nevertheless, the majority of evidence indicates

that living at high altitude, where oxygen partial pressure is relatively low (hypobaric hypoxia), seems to be associated with reduced mortality from CVD, stroke, and certain types of cancer.<sup>8</sup> The underlying mechanisms that may explain these observations are largely unexplored, but increased physical activity, decreased air pollution, and hypoxia at high altitude may be involved.<sup>8</sup> On the other hand, available evidence suggests that long-term residence at high altitude is a potential problem for chronic obstructive pulmonary disease (COPD) patients, since mortality from COPD and infections of the lower respiratory tract seem rather elevated. It seems that living at high altitude could adversely affect mortality when diseases progress.<sup>8</sup> It may be argued that moderate altitudes are more protective than high or even very high altitudes,<sup>8</sup> which can partly be attributed to chronic mountain sickness arising at higher altitudes (>3,000 m).<sup>9</sup>

A lower prevalence of impaired glucose tolerance and T2D has been found in individuals living at high altitude, namely the population of rural Aymara in Northern Chile, compared with those living at lower altitude, despite a relatively high occurrence of obesity.<sup>10</sup> In addition to a high level of physical activity (e.g. due to dependence on agriculture and time spent travelling) and possible differences in food intake, the lower ambient oxygen tension may play an important role in the lower prevalence of T2D in individuals living at high altitude.<sup>10</sup>

The supply of oxygen to organs is essential for living organisms. Importantly, available evidence indicates that alterations in ambient oxygen partial pressure, leading to changes in tissue oxygenation, may affect the metabolic profile. Interestingly, it has been demonstrated in humans that exposure to normobaric hypoxia during exercise reduces fasting glucose concentration and improves the insulin sensitivity index.<sup>11-13</sup> In line with this, exposure to moderate hypoxia (15% versus 21% O<sub>2</sub>) for 10 subsequent nights increases peripheral insulin sensitivity in obese men.<sup>14</sup> The effects of environmental hypoxia exposure seem to be mediated, at least in part, via alterations in adipose tissue and skeletal muscle metabolism.

## OXYGEN TENSION AND ADIPOSE TISSUE FUNCTION

Adipose tissue oxygen tension (AT pO<sub>2</sub>) is determined by the balance between oxygen supply via the vasculature and oxygen-consuming processes within adipose tissue.<sup>15</sup> Previous studies

have clearly shown that fasting and postprandial adipose tissue blood flow (ATBF) is decreased in obese, insulin resistant individuals compared with those who are lean and insulin-sensitive.<sup>16,17</sup> Moreover, the decrease in ATBF occurring in obesity induces a reduction in oxygen delivery to adipose tissue.<sup>16,18</sup> Therefore, it has been postulated that insufficient angiogenesis in expanding adipose tissue may lead to a relative oxygen deficit during the development of obesity.<sup>19</sup>

This hypothesis has been confirmed by several animal studies showing an increased expression of hypoxia-responsive genes, a higher abundance of hypoxic areas, and lower oxygen tension in white adipose tissue in obese versus lean animals.<sup>20-22</sup> Importantly, it should be emphasised that these studies were performed in animal models of obesity, which are characterised by rapid and massive expansion of body fat mass. In human pathophysiology, on the other hand, fat mass gain is certainly not as rapid, which implies that the reduction in oxygen supply to adipose tissue may be less severe in humans than in rodents.<sup>5,15</sup> Pasarica et al.<sup>23</sup> reported lower AT pO<sub>2</sub> in overweight and obese individuals compared with lean controls, although these findings have not been replicated thus far. In contrast, we have demonstrated an increased AT pO<sub>2</sub> in obese compared with lean, well-phenotyped individuals matched for age and sex. This higher AT pO<sub>2</sub> was observed despite the obese displaying a lower ATBF, and was associated with adipose tissue inflammation and peripheral insulin resistance.<sup>16</sup> Importantly, both studies found that physiological AT pO<sub>2</sub> values range from approximately 3-11%,<sup>16,23</sup> as assessed using either a polarographic micro Clark-type electrode<sup>23</sup> or an optochemical measurement system to continuously monitor AT pO<sub>2</sub>.<sup>16</sup> The advantage of the optochemical measurement system (range: 0-300 mmHg; accuracy: 1 mmHg), which we have recently developed,<sup>16,24</sup> is that it allows prolonged measurements of tissue pO<sub>2</sub> over a relatively large tissue area (~3-4 cm<sup>2</sup>) and it can be applied to measure pO<sub>2</sub> in any tissue (e.g. skeletal muscle) as long as insertion of a microdialysis catheter is feasible.

Because oxygen tension is determined by oxygen supply and consumption, our findings of increased AT pO<sub>2</sub> in obese individuals<sup>16</sup> suggest the presence of reduced adipose tissue oxygen consumption. Indeed, impaired mitochondrial biogenesis, morphology, and function in white and

brown adipose tissue has been described in mouse models of obesity and T2D.<sup>25</sup> Furthermore, human data indicate that adipose tissue oxygen consumption *in vivo* was lower in obese than lean individuals.<sup>16,18</sup> Moreover, it has recently been demonstrated that mitochondrial biogenesis, oxidative metabolic pathways, mitochondrial oxidative phosphorylation protein levels, and mitochondrial oxygen consumption were decreased in adipose tissue and isolated white adipocytes of obese individuals.<sup>26-28</sup> Of note, adequate mitochondrial function is essential to maintain adipose tissue function, and it protects against insulin resistance and T2D.<sup>25</sup>

These findings challenge the concept of adipose tissue hypoxia in human obesity and provide preliminary evidence that increased AT  $pO_2$  may elicit adipose tissue dysfunction and consequently insulin resistance in humans. Therefore, we recently exposed mice to chronic hypoxia or normoxia (8% versus 21%  $O_2$ , respectively) for 21 days. We found that chronic hypoxia exposure improved visceral and subcutaneous adipose tissue function,<sup>29</sup> which was evidenced by decreased adipocyte size, decreased macrophage infiltration and gene expression of inflammatory markers, and increased expression of mitochondrial function and biogenesis markers.<sup>29</sup> These findings suggest that reducing AT  $pO_2$  may exert beneficial effects on adipose tissue function and, consequently, insulin sensitivity. However, these findings need to be confirmed in humans.

## OXYGEN TENSION AND SKELETAL MUSCLE GLUCOSE UPTAKE

In addition to the effects of oxygen tension on adipose tissue function, there is evidence that hypoxia may also affect skeletal muscle glucose uptake and mitochondrial biogenesis. As such, hypoxia exposure might mimic the effects of exercise. More specifically, it has been shown that acute hypoxia exposure stimulates glucose transport in isolated muscle strips from insulin resistant humans.<sup>30</sup> Interestingly, the hypoxia-induced stimulation of glucose uptake in these muscle strips was comparable between those from lean and obese individuals, as well as those from obese patients with T2D.<sup>30</sup> However, it should be noted that 'normoxia' and 'hypoxia' reflected non-physiological conditions (95% versus 0%  $O_2$ , respectively). Furthermore, acute hypoxia exposure during exercise improved the effect of exercise

on glucose tolerance compared with exercise under normoxic conditions.<sup>11</sup> In the insulin resistant muscle, the major defect is in insulin-mediated glucose uptake. However, the ability of hypoxia to induce skeletal muscle glucose uptake to the same extent in insulin-sensitive and insulin resistant muscle<sup>30</sup> indicates that the hypoxia-induced glucose uptake pathway is still intact in the insulin resistant muscle. Interestingly, hypoxia appears to stimulate skeletal muscle glucose transport through adenosine monophosphate-activated protein kinase and  $Ca^{2+}$ /calmodulin-dependent protein kinase-dependent pathways in rodents.<sup>31,32</sup> In line with this, it has recently been shown that exposure of human myotubes to 15%  $O_2$  increased basal but not insulin-stimulated glucose uptake compared with 21%  $O_2$ .<sup>14</sup> Furthermore, hypoxia exposure increased the expression of the master regulator of mitochondrial biogenesis and function, peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$ , in C2C12 myotubes.<sup>33</sup> In conclusion, several rodent and human studies have indicated that hypoxia may improve skeletal muscle glucose uptake, mitochondrial biogenesis and function, and whole-body glucose homeostasis.

## BENEFICIAL EFFECTS OF MODERATE HYPOXIA EXPOSURE

Weight loss and increased physical activity are recommended to reduce cardiometabolic risk in obese humans. However, this is not easily achieved by all individuals and, therefore, alternative or additional strategies to improve cardiometabolic health are warranted. Although the effects of the severity and duration of oxygen exposure have not been studied extensively, it seems that moderate hypoxia exposure (9-16%  $O_2$ ) using a limited number of cycles (3-15 cycles per day) may have beneficial effects on neurodegenerative diseases, the immune system, body weight, CVD, exercise performance, and, importantly, lipid and glucose metabolism.<sup>34</sup>

Several studies have examined the effect of a combined hypoxia and exercise intervention on body weight. Interestingly, a larger decrease in body fat content was found when patients were exposed to moderate hypoxia rather than normoxia during the exercise sessions.<sup>35-38</sup> In line with this, it has been shown that hypobaric moderate hypoxia exposure induces a reduction in body weight together with increased metabolic rate in obese patients.<sup>38</sup> In addition, exercising

under hypoxia (approximately 14–15% O<sub>2</sub>) evoked a more pronounced improvement in insulin sensitivity and glucose tolerance compared with normoxia.<sup>12,13</sup> More recently, it has been found that an 8-month exercise intervention programme reduces body weight, body mass index, and waist-hip ratio, and improves performance peak and systolic blood pressure to the same extent in those who completed the exercise sessions under moderate hypoxia as those who exercised under normoxic conditions.<sup>39</sup> However, it cannot be excluded that the effects of exercise per se may have masked beneficial effects of moderate hypoxia exposure. Furthermore, metabolic parameters, including glycosylated haemoglobin, glucose, triacylglycerol, and cholesterol concentrations, were not significantly altered in either group after the training programme.<sup>39</sup>

Importantly, moderate hypoxia exposure may have beneficial effects on glucose homeostasis. For example, glucose disposal was increased after acclimatisation to high altitude (4,300 m) compared with sea level in healthy humans.<sup>40</sup> In addition, normobaric intermittent hypoxia exposure decreased plasma glucose concentrations in rodents.<sup>41</sup> More recently, the effect of moderate hypoxia exposure on insulin sensitivity has been studied in obese humans. Interestingly, 10 consecutive nights of moderate hypoxia exposure (approximately 10 hours exposure/night to approximately 15% O<sub>2</sub>) significantly improved peripheral insulin sensitivity and tended to reduce AT pO<sub>2</sub>.<sup>14</sup> Therefore, it is tempting to postulate that the decrease in AT pO<sub>2</sub> observed in this study may have contributed to improved peripheral insulin sensitivity after moderate hypoxia exposure.<sup>42</sup> Furthermore, *in vitro* exposure of human myotubes derived from these individuals to 15% O<sub>2</sub> improved basal but not insulin-stimulated glucose uptake compared with normoxia exposure, supporting direct effects of moderate hypoxia exposure on skeletal muscle glucose uptake. Notably, acute mountain sickness symptoms (e.g. headache, nausea) may occur above approximately 2,500 m (<15% O<sub>2</sub>) and adverse events should be carefully monitored when exposing individuals to (moderate) hypoxia.

Taken together, these studies suggest that normobaric moderate hypoxia exposure may elicit beneficial effects on glucose homeostasis (Figure 1). Nevertheless, most human *in vivo* studies performed thus far have either examined the effects of acute hypoxia exposure,<sup>12</sup> used

surrogate markers of insulin sensitivity,<sup>12</sup> or did not include a control group,<sup>14</sup> and information on underlying mechanisms in relevant organs is very limited.<sup>10,12,14,40</sup> Therefore, this promising treatment avenue needs to be explored in more detail in humans.

## DETRIMENTAL EFFECTS OF SEVERE INTERMITTENT HYPOXIA IN OBSTRUCTIVE SLEEP APNOEA SYNDROME PATIENTS

Obstructive sleep apnoea syndrome (OSAS) is a condition characterised by periodic collapse (obstruction) of the upper airway during sleep, resulting in episodes of severe hypoxia. OSAS affects 4–24% of men and 2–9% of women in the USA.<sup>43,44</sup> However, OSAS prevalence is >50% in the obese population.<sup>43,44</sup> Indeed, obesity is a major risk factor for OSAS, which results in severe intermittent hypoxia (SIH) as it promotes enlargement of the tissue surrounding the airway, leading to narrowing of the airway.<sup>43,45</sup> It is well known that OSAS is a risk factor for the development and progression of cardiometabolic diseases, and exacerbates the metabolic syndrome. This is exemplified by the findings that obese OSAS patients have an increased risk of CVD, sympathetic activation, systemic inflammation, and endothelial dysfunction compared with obese individuals without OSAS.<sup>46,47</sup> Furthermore, epidemiological studies have shown that an increased severity of OSAS is associated with progressive worsening of insulin resistance and other characteristics of the metabolic syndrome.<sup>48,49</sup>

It has been proposed that impairments in lipid and glucose metabolism substantially contribute to the adverse clinical outcomes related to OSAS.<sup>50</sup> Interestingly, it has been demonstrated that SIH exposure reduces liver, muscle, and AT pO<sub>2</sub> *in vivo*, and impairs glucose homeostasis in lean mice.<sup>51</sup> In line with this, SIH has been found to acutely induce insulin resistance due to decreased skeletal muscle glucose utilisation in rodents.<sup>52</sup> Of note, lean mice exposed to intermittent hypoxia for several days do not show induction of insulin resistance, in contrast to genetically or diet-induced obese mice.<sup>53</sup>

Systemic low-grade inflammation is increased in OSAS patients.<sup>54</sup> Furthermore, SIH may increase reactive oxygen species.<sup>55,56</sup> In addition to oxidative stress and inflammation, SIH leads to sympathetic system activation, which stimulates

gluconeogenesis in the liver and may thereby contribute to impaired glucose homeostasis.<sup>57</sup> Although it cannot be excluded that other factors, including sleep fragmentation, play an important role in the adverse effects of OSAS, SIH is thought to be a major determinant of the detrimental metabolic and cardiovascular effects.

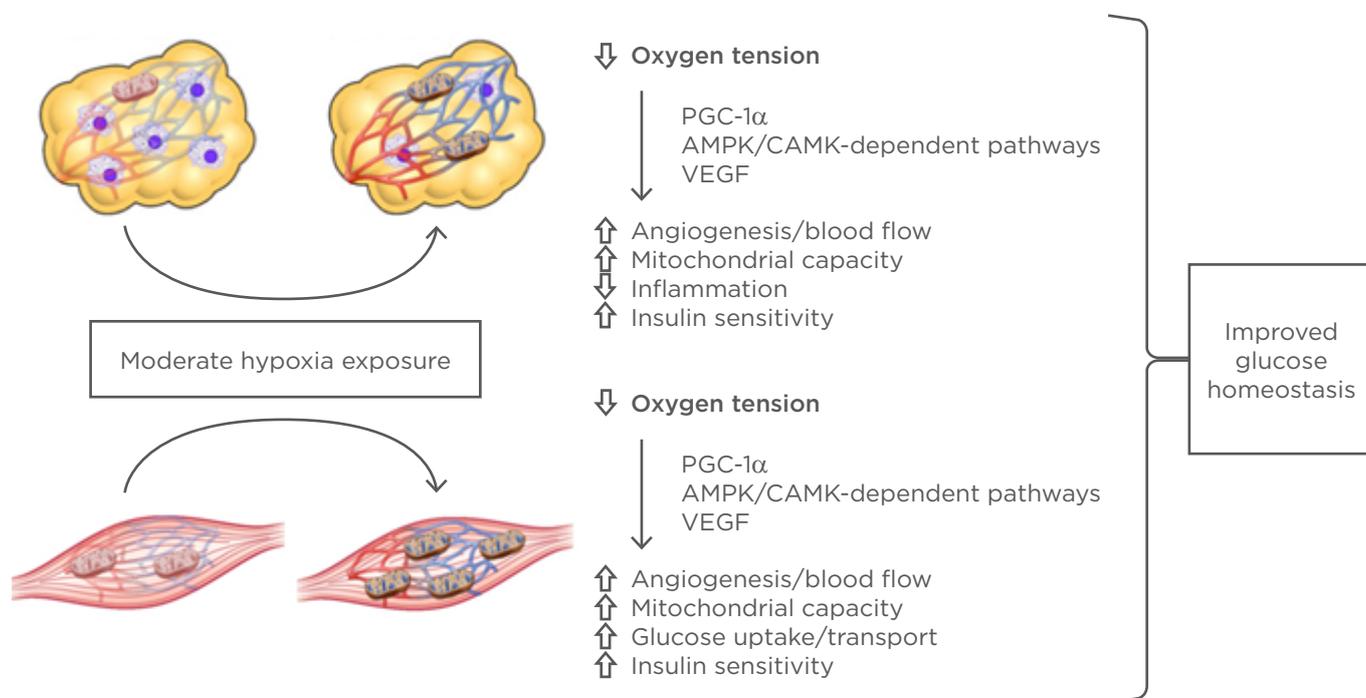
Continuous positive airway pressure (CPAP) is the first-line treatment for OSAS. CPAP, which delivers a stream of compressed air via a mask in order to keep the airway open under air pressure and thereby reduce or prevent nocturnal oxygen dips,<sup>58</sup> may have beneficial effects on lipid profile and glucose homeostasis. Strikingly, 3 months of CPAP treatment reverses several metabolic abnormalities in OSAS patients,<sup>59</sup> but the underlying mechanisms are not fully understood.

Taken together, OSAS is associated with increased metabolic and cardiovascular risk, and several studies have suggested that this is related to the severity of the hypoxic episodes to which these patients are exposed.

## CONCLUSION AND PERSPECTIVE

The prevalence of obesity, CVD, and T2D is increasing at an alarming rate. Adopting a healthy lifestyle (e.g. healthy diet, increasing physical activity) can help to prevent or delay the onset of CVD and T2D. However, additional strategies are needed to mitigate the development of these chronic diseases in high-risk individuals.

There is substantial evidence that altered AT  $pO_2$  is related to impaired adipose tissue function.



**Figure 1: Proposed effects of moderate hypoxia exposure on adipose tissue and skeletal muscle that may contribute to improved glucose homeostasis.**

A pro-inflammatory phenotype, impaired mitochondrial capacity, and insulin resistance characterise dysfunctional adipose tissue in human obesity. Furthermore, skeletal muscle mitochondrial capacity, glucose uptake, and insulin sensitivity are decreased in obese insulin resistant humans. Moderate hypoxia exposure may decrease oxygen tension in adipose tissue and skeletal muscle, thereby increasing mitochondrial capacity, glucose uptake, and local insulin sensitivity, and reducing adipose tissue inflammation. Proposed molecular pathways that may mediate the effects of moderate hypoxia exposure in adipose tissue and skeletal muscle include PGC-1 $\alpha$ , AMPK/CAMK-dependent pathways, and VEGF. Together, this may contribute to improved glucose homeostasis in humans.

PGC-1 $\alpha$ : peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$ ; AMPK: adenosine monophosphate-activated protein kinase; CAMK: Ca<sup>2+</sup>/calmodulin-dependent protein kinase; VEGF: vascular endothelial growth factor.

Likewise, hypoxia seems to improve skeletal muscle glucose metabolism. Therefore, modulation of ambient oxygen partial pressure, thereby affecting oxygen supply to key metabolic organs, may have positive cardiometabolic effects. Indeed, it has been demonstrated that moderate hypoxia exposure may improve adipose tissue function and skeletal muscle glucose uptake. Therefore, it is tempting to postulate that exposure to moderate hypoxia may be a promising strategy to reverse insulin resistance and to improve cardiometabolic health in obese individuals (Figure 1). However, OSAS patients are at increased metabolic and cardiovascular risk, which seems to be related to

episodes of SIH that occur during sleep due to airway obstruction. The exposure regimen (e.g. severity and pattern of exposure) may therefore be critical regarding effects on metabolic health, and the underlying mechanisms responsible for the potential insulin-sensitising effect of moderate hypoxia exposure remain to be elucidated. Clinical studies in well-phenotyped humans are needed to further investigate the effects of different moderate hypoxia exposure regimens on insulin sensitivity, and lipid and glucose homeostasis. In addition, we need to obtain a better understanding of the underlying mechanisms in key metabolic organs, including adipose tissue and skeletal muscle.

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## Acknowledgements

The authors would like to thank all colleagues who have contributed to the studies performed by our research group, and would like to thank the Dutch Diabetes Research Foundation (Innovative Pilot Grant to G.H.G.) and European Foundation for the Study of Diabetes (Clinical Research Grant to G.H.G.) for financial support.

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