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Intermittent Hypoxia as an Interventional Strategy for Impaired Fasting Blood Glucose: a Systematic Review

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Abstract

The aim of this systematic review is to analyse the current evidence reported in the literature on the efficacy of resting in normobaric hypoxia as a potential intervention for patients with impaired fasting blood glucose. Available databases was searched, under the PRISMA guidelines, throughout to the end of August 2017. A total of four empirical studies (out of 3281 filtered) were identified as eligible for the review. Two studies were on the acute effects of one-hour exposure to moderate hypoxia, and reported a reduction of blood glucose by 0.74 to 2.1 mM. The other two studies were on the effects of repeated exposure with nine to ten sessions in two to three weeks, however did not shown sustained decrease in fasting blood glucose. These studies employed self-controlled design with relatively small numbers of participants (n= 6-18). Similar findings were also reported in studies on the effects of exercising in hypoxia with single bout or several weeks of intervention. Further research, particularly randomised controlled clinical trials, is required to determine the efficacy and hormetic dosage range of long-term IH intervention for pre-diabetes and type 2 diabetes, and to elucidate the underlying mechanisms of the treatment effects.

Keywords: Normobaric hypoxia, type 2 diabetes, impaired fasting blood glucose, insulin resistance, hormesis

1. Introduction

A major characteristic associated with type 2diabetes (T2D) is hyperglycaemia (Röder, Wu, Liu, & Han, 2016). A healthy glucose homeostasis maintains fasting blood glucose (FBG) levels in the range of 4–6 mM, with concentrations of 6.1–6.9 mM indicative of an impaired fasting glucose (IFG), and ≥7.0 mM standing as the current diagnostic criterion for diabetes (World Health Organization, 2016). The compromised glycaemic state, i.e. impaired glucose homeostasis, rises due to an imbalance in the normal physiological maintenance of blood sugar levels, managed largely via the action of glucagon and insulin (INS) (Röder et al., 2016). Literature attributes the cause of hyperglycaemia to an increased insulin resistance (IR) in adipose, muscle and hepatic tissues (Abranches, Oliveira, Conceição, & Peluzio, 2015) that reduces the rate of glucose clearance from the blood stream. This is coupled with a reduced pancreatic β-cellmass which, after an initial compensatory hyperinsulinemia, ultimately results in lowered insulin secretion (Triplitt, 2012).

Approaches recommended for prevention and management of diabetes include regular participation of exercise, healthy diet, abstinence from smoking, and lowering blood pressure and lipids (Ley, Hamdy, Mohan, & Hu, 2014; World Health Organization, 2016; Zanuso, Jimenez, Pugliese, Corigliano, & Balducci, 2010), often in combination with pharmaceutical interventions (Hassali, Nazir, Saleem, & Masood, 2015).

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Despite the established interventional strategies currently recommended by health organisations and governments, the prevalence of diabetes has continued to rise over the last decade. Therefore, continuous efforts in research are needed for more effective prevention and management strategies for diabetes. For example, adequate exercise and physical activity have been proven to be an effective strategy for prevention and management of T2D and obesity (Hordern et al., 2012), however there are individuals who are unable to participate in regular exercise due to physical impediments (Assari, Lankarani, & Lankarani, 2014; Gregg et al., 2002) highlighting the need for alternative means of intervention.

There have been suggestions that intermittent exposure to moderate levels of hypoxia may have beneficial effects on glucose control and therapeutical values to metabolic diseases (Kong, Zang, & Hu, 2014; Mackenzie & Watt, 2016; Navarrete-Opazo & Mitchell, 2014; Wee & Climstein, 2015). Hypoxiais defined as a reduction in the partial pressure of oxygen (pO_2) resulting in alveolar, blood or tissue oxygen deprivation (Song, Fang, Greenberg, & Liu, 2015). This can be achieved via a variety of modalities, including exposure to inhaled gas with a lower than sea level of pO_2, e.g. when the fraction of oxygen in inspired air (FiO_2) is less than 0.209 but at normal barometric pressure (i.e. normobaric hypoxia), or at high altitudes where the barometric pressure and the pO_2 are lower than that at the sea level (i.e. hypobaric hypoxia) (Serebrovskaya & Xi, 2016). Intermittent hipoxia (IH) refers to episodic exposure to reductions in O_2 in the inspired air separated by periods of normoxia (Serebrovskaya & Xi, 2016).

Intermittent hypoxia can be experienced in certain health conditions, such as chronic obstructive pulmonary disease (COPD), asthmatic episodes and obstructive sleep apnoea (OSA). There seems to exist a dichotomous representation of IH in the literature: chronic exposure to severe levels of hypoxia (e.g., 0.02-0.08 FiO_2), such as in OSA, is positively associated with the development of metabolic complications, while acute exposure to moderate levels of hipoxia (e.g., 0.09-0.16 FiO_2) seems to induce beneficial patient outcomes (Navarrete-Opazo & Mitchell, 2014). Research indicates that intermittent exposure to severe hypoxic situations in such health conditions has the effect to decrease glucose effectiveness (Louis & Punjabi, 2009); impair β-cell function, while increase pancreatic oxidative stress (Polak et al., 2013); advance fatty liver obesity (Paschetta et al., 2015); as well as increase IR (Wang, Yu, Yue, Zeng, & Cui, 2015). Due to the severe level and the long-term hypoxia experienced in OSA and COPD, investigations into IH associated with these pathologies fall outside the scope of this review. A recent review is available that provides a good analysis and summary of current literature in this area (Mateika & Komnenov, 2017).

Intermittent exposure to moderate hypoxia was identified in the former Soviet Union in the 1930's as having therapeutic benefit as a preventative measure for certain immunological diseases, as well as enhancing performance of aircraft pilots (Serebrovskaya, 2002). There have been reviews on the effects of exposure to high altitude on glucose homeostasis (Hessien, 2013; Woolcott, Ader, & Bergman, 2015), however their focus was on the effects of long-term sustained exposure to hypobaric hypoxia, in contrast to the intermittent exposure to simulated pO_2 as at altitude (normobaric hypoxia provided by hypoxia chambers or hypoxicators) that may have better clinical practicality.

There have been reviews in the literature indicating that IH may have benefits to cardiovascular and autonomic function, metabolic function, respiratory motor plasticity and cognitive function, lipid profile, weight control, and immune function, with recognition of possible detrimental effects depending on the dose (Almendros, Wang, & Gozal, 2014; Kayser & Verges, 2013; Mateika, El-Chami, Shaheen, & Ivers, 2015; Navarrete-Opazo & Mitchell, 2014; Wee & Climstein, 2015). Furthermore, exercise combined with IH has shown additive beneficial effects (Brinkmann, Bloch, & Brixius, 2017; Kong et al., 2014; Wiesner et al., 2010). It has been suggested in the literature that hypoxia therapy without exercise would also provide an alternative intervention for patients with limited capacityin participating in regular exercise (Leone & Lalande, 2017). However, limited evidence has been reported in the literature on the effects of hypoxia intervention on IFG. The aim of this systematic review is to examine the current evidence presented in the literature for the efficacy of applying moderate level of normobaric hypoxia, without a combination with exercise, as a means of intervention for IFG, and identify the gaps in knowledge for future research and practice in this area.

2. Material and methods

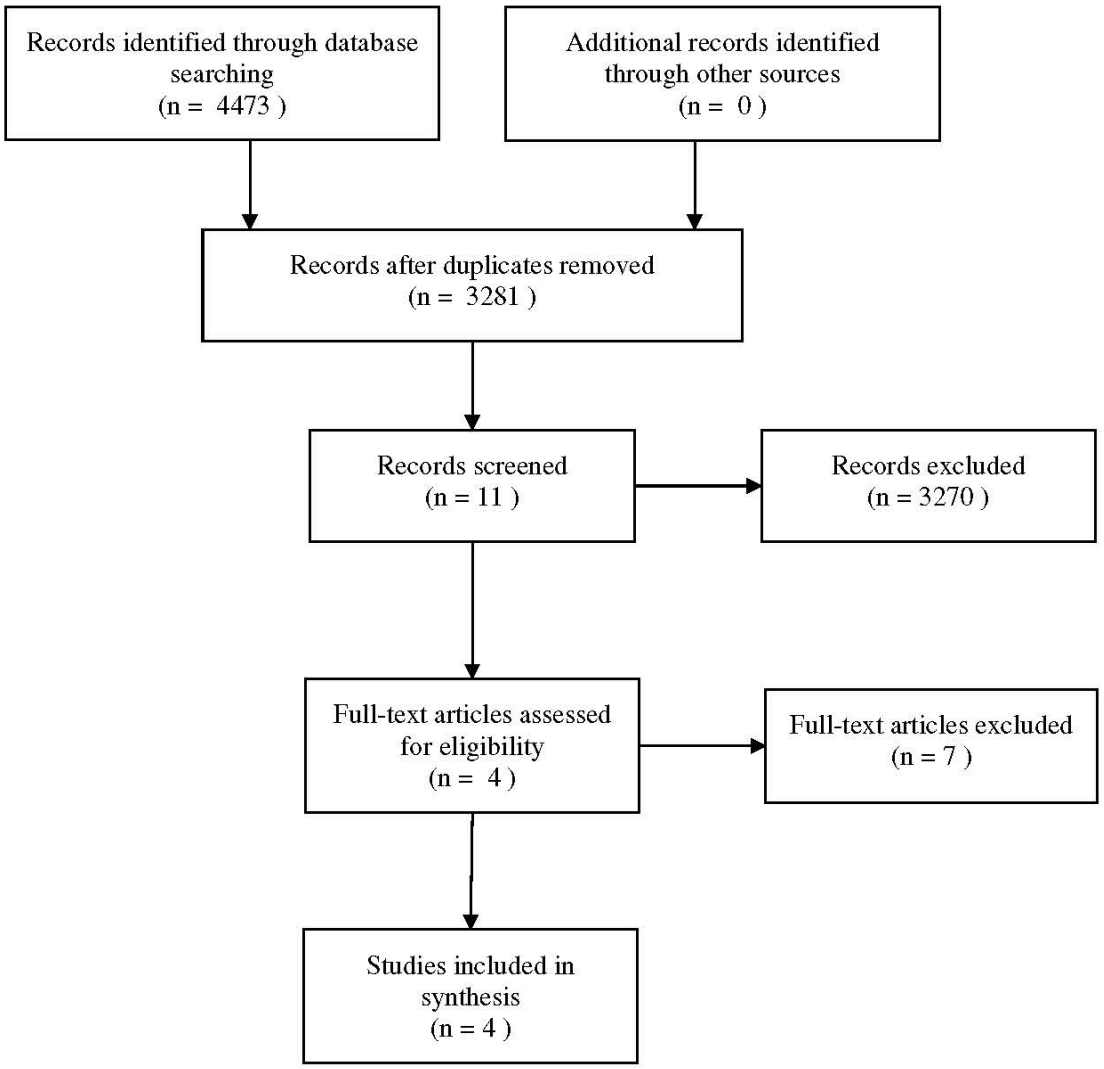
2.1. Data Sources and Searches.

The databases of AMED, CINAHL, Health Source, MEDLINE, PsycARTICLES, Psychology and Behavioural Sciences Collections, PsycINFO, PubMed, ScienceDirect, Scopus, and SPORTDiscus were searched throughout to the end of August 2017, utilising a search strategy with the keywords or strings in any fields of the

articles as filters to select eligible articles, including "hypoxia" (or "hypoxic") AND "type 2 diabetes" (or "type 2 diabetes mellitus" or "t2dm"), OR "hyperglycaemia" (or "hyperglycemia" or "hyperglycaemic" or "hyperglycemic"), OR "obesity" (or "obese" or "overweight"), OR "metabolic syndrome", while excluding articles (AND NOT) with "obstructive sleep apnoea" (or "OSA"), OR "chronic obstructive pulmonary diseases" (or "COPD"), OR "apnoea", OR "animal" (or "rat" or "mouse" or "mice").

2.2. Study Selection. Only full text empirical research articles on human patients were included, and books, book chapters, review articles, notes, letters, communications with editor, responses to comments, conference abstracts, and tables of contents, were excluded. Studies that did not investigate normobaric hypoxia, e.g., residents and residential camps at altitude, were also removed.Finally, only the studies that investigated participants with IFG, i.e. the baseline FBG >6.0 mM, or impaired glucose tolerance (IGT), i.e. blood glucose (GLU) >7.8 mM at 2 h post ingestion of 75 g glucose in oral glucose tolerance test (OGTT) (World Health Organization, 2016), were included in this review. Figure 1 summaries the literature search strategy with reference to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009).

Figure 1. Flow chat of literature search.



2.3. Data Extraction and Quality Assessment. All of the reviewed articles were evaluated against a modified 'Downs & Black' checklistfor the strength of the evidence presented (Downs & Black, 1998). The original Downs & Black checklist had 27 items with a maximum possible score of 32 (item 5 had up to 2 points and item 27 had up to 5 points). Item 27 was modified to "one point awarded if a significant difference was found or a sample size calculation was completed" to avoid ambiguity (Morton, Barton, Rice, & Morrissey, 2014). The modified version utilised in this review had a maximum score of 28, with each article was assigned a grade of "excellent" (24-28 points), "good" (19-23 points), "fair" (14-18 points) or "poor" (<14 points) (O'Connor et al., 2015).

3. Results

The ensuing literature search was run, yielding a total of 11full text articles that investigated the effects of hypoxia intervention in participants with type 2 diabetes or pre-diabetes (Costalat, Lemaitre, Tobin, & Renshaw, 2017; Duennwald, Gatterer, Groop, Burtscher, & Bernardi, 2013; Fuller & Courtney, 2016; Gatterer et al., 2015; Hessien, 2013; Mackenzie, Elliott, Maxwell, Brickley, & Watt, 2012b; Mackenzie, Maxwell, Castle, Brickley, & Watt, 2011; Mackenzie et al., 2012a; Schreuder, Nyakayiru, Houben, Thijssen, & Hopman, 2014; Serebrovska et al., 2017; Shatylo, Serebrovska, Gavalko, Egorov, & Korkushko, 2016). Further screening confirmed eligibility of four articles for inclusion in this review. These studies reported the effects of hypoxia intervention alone or included a 'rest in hypoxia' group. One of these studies recruited overweight and obese participants with the mean FBG 5.86±1.23 mM, however the reported FBG on the first day of intervention was 6.21±1.62 mM, therefore was included in this review (Costalat et al., 2017). The seven articles that were thought ineligible included four studies on the effects of exercise in hypoxia (Gatterer et al., 2015; Mackenzie et al., 2012b; Mackenzie et al., 2012a; Schreuder et al., 2014), one cross sectional study that compared IFG between the residents at high and low altitudes (Hessien, 2013), and two interventional studies with participants' baseline FBG <6.0 mM(Fuller & Courtney, 2016; Shatylo et al., 2016).

The four eligible studies are summarised in Table 1. The average age of the participants was from 56.2 to 66.4 years, including a total of 31 men and 15 women (excluding healthy controls). The average body mass index (BMI) of the participants was from 27.3 to 33.2 kg/m² that can be categorized as pre-obese (25.0-29.9) or obese (30+)(World Health Organization, 2000). Two of these studies reported the acute changes in GLU after a single bout of 60 min exposure to hypoxia, while the other two reported the effects of repeated exposure to IH with nine to ten sessions in two to three weeks. None of these studies found any adverse events during hypoxia intervention.

For the single bout exposure, Mackenzie et al. (2011) compared the effects of 1) rest in normoxia (as control), 2) rest in hypoxia with FiO_2 0.146, 3) exercise in normoxia, and 4) exercise in hypoxia with FiO_2 0.146, in T2D patients (n=8). The GLU reduced by 0.74±0.14 mM (P=0.002) from the pre to post 60 min of continuous 'rest in hypoxia', that was greater (P=0.014) than that under the 'rest in normoxia' condition (decreased by 0.23±0.16 mM, P=0.181) (Mackenzie et al., 2011). Duennwald et al. (2013), in a single blind studywith 14 T2D patients, compared the effects of IH exposure to FiO_2 0.13 with five cycles of 6 min hypoxia followed by 6 min normoxia (a total of 60 min), with a placebo trial (normoxia) on a separate day. The authors reported a significantly decreased GLU from 8.3±0.9 mMpre to 6.2±0.6 mM post the hypoxia exposure (2.1 mM reduction, P<0.05), while no significant change was found in the placebo day (pre 7.1±0.8vs. post 6.3±0.5 mM, i.e. 0.8 mM reduction) (Duennwald et al., 2013).

For the effects of repeated exposure to hypoxia, Serebrovska et al. (2017) compared the responses to a hypoxia intervention between individuals with pre-diabetes (IFG or IGT) and healthy controls. Both the pre-diabetes group (n=11) and control group (n=7) received hypoxia intervention at FiO_2 0.12, with four cycles of 5 min hypoxia followed by 5 min normoxia (a total of 40 min) in each session, three sessions per week for three weeks. The pre-diabetes group showed non-significant decrease in FBG one day post, but significant decrease one month post the intervention (Pre 5.6±0.6 mM; 1 d 5.4±0.7 mM;and 1 m 5.2±0.4 mM, P<0.05; 0.4 mM reduction). The GLU in OGTT at 2 h post ingestion of 75 g glucose showed a significant decrease in the pre-diabetes group (Pre 7.9±1.5 mM; 1 d 7.0±1.9 mM, P<0.05;and 1 m 6.4±1.0 mM, P<0.01; 1.5 mM reduction). The control group showed no change during the same period (Serebrovska et al., 2017). Costalat et al. (2017) investigated the effects of five sessions in normoxia followed by 10 sessions of IH on a group of overweight or obese participants (n=6) in a single blind trial. Each hypoxia session included 70 min of repeated cycles of hypoxia at FiO_2 0.10 until SpO_2 reached 70% followed by normoxia, then hypoxia restarted when SpO_2 recovered to 95%. The authors reported that the GLU decreased only during the first IH session, from pre 6.21±1.62 mM to post 5.32±1.03 mM (P<0.05; 0.89 mM reduction), but no sustained changes during the following sessions, neither during the normoxia sessions (Costalat et al., 2017).

Table 1. Summary of literature on the effects of hypoxia intervention on impaired fasting blood glucose in patients

References	Participants	Design and Protocol	Blood Glucose Changes	Selected Outcome Measures	Quality Scores
Mackenzie et al. (2011)	T2D • Age: 58±4 yr Gender and number: M 8 • Baseline FBG: 8.4±1.8 mM • BMI: 29.2±6.7	• Self-controlled • Single bout of 60 min, continuing exposure in hypoxia chamber • Interventions: 1) Rest in normoxia 2) Rest in hypoxia, FiO_2 0.146, safety threshold $SpO_2$70% 3) Exercise at 90% lactate threshold in normoxia 4) Exercise at 90% lactate threshold in hypoxia, FiO_2 0.146	• Significant reduction in GLU post all interventions, except 'rest in normoxia'	• Significant improvement inINS sensitivity post interventions compared with the 'rest in normoxia' condition • Additive beneficial effect of 'exercise in hypoxia' compared with 'exercise in normoxia'	18
Duennwald et al. (2013)	T2D • Age: 59.3±1.5yr Gender and number: M 11, F 3 • Baseline FBG: 7.7±0.6 mM • BMI: 29.0±1.0	• Self-controlled, single-blind • Single bout of 60 min, intermittent 6 min hypoxia: 6 min normoxia, using a hypoxicator • Interventions: 1) Rest in hypoxia, FiO_2 0.13, Safety threshold $SpO_2$80% 2) Rest in normoxia	• Significant decrease in GLU immediately post, and at 6 h post, but non-significant at 3 h post (due to effect of a meal), the hypoxia session • Non-significant change in GLU post the normoxia session with a significant increase at 3 h post, due to effect of a meal	• The hypoxia intervention resulted significant less post-prandial GLU increase than the normoxia session	19
Serebrovska et al. (2017)	Pre-diabetes group • Age: 66.4±5.2 yr Gender and number: M 5, F 6 • Baseline FBG: 5.6±0.6 mM; or OGTT 2 h: 7.9±1.5 mM • BMI: 33.2±5.6 Healthy group • Age: 58.7±11.8 yr Gender and number: M 3, F 4 • Baseline FBG: 4.6±0.4 mM; OGTT 2 h: 5.3±1.5 mM • BMI: 27.3±6.4	• Self-controlled, also compared with a healthy group • Intermittent hypoxia at $FiO_2$0.12 via a hypoxicator • 5 min hypoxia : 5 min normoxia, 4 cycles per session (40 min), 9 sessions in 3 weeks	• Pre-diabetes group showed non-significant decrease in FBG 1 day after the intervention, but significant decrease 1 month post the intervention • No significant change in the healthy control group	• OGTT 2 h showed significant improvement 1 day and 1 month post the intervention	17
Costalat et al. (2017)	Overweight/Obese • Age: 56.2±10 yr Gender and number: M 4, F 2 • Baseline FBG: 5.86±1.23 mM (pre hypoxia intervention 6.21±1.62 mM) • BMI: 30.6±1.4	• Self-controlled, single blind • 70 min repeated cycles of hypoxia at FiO_2 0.10 (to safety threshold SpO_2 70%) and re-oxygenation (to SpO_2 95%) using a hypoxicator • 5 sessions(in one week) normoxia • 10 sessions (in two weeks) intermittent hypoxia intervention	• Significant decrease in GLU after the first IH session. • No change in GLU after a single normoxia session • No significant change in GLU post 2 weeks of IH intervention	• Significant decrease in LDLcand LDLc/HDLc ratio from pre to post 10 sessions of intermittent hypoxia	15

BMI: body mass index (mass kg/height m^2);FBG: fasting blood glucose; GLU: blood glucose; HDLc: high density lipoprotein cholesterol; IH: intermittent hypoxia; INS: insulin concentration; IR: insulin resistance;LDLc: low density lipoprotein cholesterol; OGTT: oral glucose tolerance test; SpO_2: blood saturation of oxygen; T2D: type 2 diabetes

4. Discussion

Although it has been suggested that normobaric hypoxia could be used as a potential intervention for health conditions including pre-diabetes and type 2 diabetes, this systematic review only identified four empirical studies that actually examined the efficacy of 'rest in hypoxia' on blood glucose in pre-diabetes and T2D participants in the current literature (Costalat et al., 2017; Duennwald et al., 2013; Mackenzie et al., 2011; Serebrovska et al., 2017).

From research design and methodology viewpoint, all these four studies were self-controlled, i.e. the same participants were given hypoxia or placebo treatment for comparison, except one study that included a healthy control group (Serebrovska et al., 2017). Two of the studies employed a single blind approach (Costalat et al., 2017; Duennwald et al., 2013) but there was no randomised controlled trial. The number of patients recruited in these studies was relatively small, from 6 to 18, and none of the studies addressed whether such numbers and the research design had sufficient statistical power for the effects under concern. The modified Downs and Black (1998) checklist (O'Connor et al., 2015) was used to assess the quality of the evidence, and these four studies were scored from 15 to 19 (Table 1), i.e. in the range of 'fair' (Costalat et al., 2017; Mackenzie et al., 2011; Serebrovska et al., 2017) or 'good' (Duennwald et al., 2013).

Based on the studies included in this review, there appear to be consistently evident that a single bout exposure to moderate hypoxia has an acute effect of decreasing GLU in individuals with IFG or IGT (Costalat et al., 2017; Duennwald et al., 2013; Mackenzie et al., 2011). The GLU decreased in a range of 0.74 to 2.1 mM on average after 40 min to 70 min exposure to moderate hypoxia (FiO_2 0.10 to 0.147). However, the reported effects of repeated exposure to IH on GLU were equivocal. Costalat and associates (2017) reported an acute reduction in GLU after one bout exposure, but no sustained changes in the following nine sessions of IH. Serebrovska and associated (2017) reported no significant decrease in FBG one day post the three weeks intervention program (nine sessions of 40 min), but a significant decrease in FBG one month post the intervention. Therefore, there has been no solid evidence to date suggesting that repeated exposure to moderate hypoxia at rest is an effective intervention for IFG or IGT. Further research, particularly with randomised controlled clinical trials, is needed to rigorously examine the effects of long-term IH intervention on IFG or IGT, without a combination with other types of interventions, such as exercise or diet programs.

Although the effect of exercise in hypoxia is not the focus of this review, it is worthwhile to mention that the literature search also identified two reports on the acute effects of a single bout of exercise in hypoxia (Mackenzie et al., 2012b; Mackenzie et al., 2012a) and two reports on the repeated sessions of exercise in hypoxia on IFG or IR (Gatterer et al., 2015; Schreuder et al., 2014) (Table 2). Mackenzie et al. (2012a, 2012b) investigated the acute effects of one bout cycling exercise on GLU and IR in T2D patients (n=8), at different intensities and durations in a hypoxia chamber with FiO_2 0.147. The authors reported that GLU decreased immediately post and in 24 h to 48 h post the intervention, together with improvement in IR in response to the exercise protocols (Mackenzie et al., 2012b; Mackenzie et al., 2012a).Schreuder et al. (2014) reported a randomised controlled trial for T2D patients in which 19 participants were randomly allocated to a hypoxia or a normoxia training group and performed cycle exercise in a chamber with FiO_2 0.165 or normoxia, 45 min per session, three sessions per week for eight weeks. The authors found no significant change in FBG between and within the two groups, neither in insulin resistance measurements (Schreuder et al., 2014). Gatterer et al. (2015) also run a randomised controlled trial in obese patients with IFG in which 32 participants were randomly allocated to two groups. One group trained in a chamber with 90 min exercise plus 90 min rest per session in hypoxia with FiO_2 0.122, while the other group trained in normoxia, two sessions per week, for eight months. The authors reported no significant differences in FBG between and within the two groups pre and post the intervention (Gatterer et al., 2015). These studies were scored 20-21 as 'good' (Gatterer et al., 2015; Schreuder et al., 2014) or 18 as 'fair' (Mackenzie et al., 2012b; Mackenzie et al., 2012a) in respect the quality of evidence, according to the modified Downs and Black checklist used in this review (O'Connor et al., 2015). These reports further underscore the acute effects of moderate hypoxia on IFG, however add to the ambiguity of the efficacy of long-term IH as a potential intervention for IFG.

The controversial evidence reported in the literature, for both hypoxia alone and exercise in hypoxia interventions, could be attributed to the characteristics of the participants and the designs of the interventional programs. In this review, we have rigorously screened the literature and focused on the participants with IFG, IGT or T2D as defined by World Health Organization and International Diabetes Federation (World Health Organization,

2016), while some previous reviews or studies may have included participants with various blood glucose profiles that were not compliant with the World Health Organization criteria for IFG or IGT, or regarded as healthy.

Table 2. Summary of literature on the effects of exercise in hypoxia on impaired fasting blood glucose in patients

References	Participants	Design and Protocol	Blood Glucose Changes	Selected Outcome Measures	Quality Scores
Mackenzie et al. (2012a)	T2D • Age: 58.7±2.2yr Gender and number: M 8 • Baseline FBG: 8.1±0.7 mM • BMI: 28.3±2.1	• Self-controlled • Single bout of 60 min cycle exercise, follow-up at 24 h and 48 h • Interventions: 1) HyEx60: Continuous 60 min exercise at 90% lactate threshold in hypoxia room with FiO_2 0.147 2) Hy5:5: 5 min exercise at 120% lactate threshold: 5 min rest for 6 cycles in hypoxia room with FiO_2 0.147 3) Nor5:5: 5 min exercise at 120% lactate threshold: 5 min rest for 6 cycles in normoxia	• Significant decrease in GLU immediately post all three interventions • Significant decrease in FBG 24 h post all three interventions • Non-significant decrease in FBG 48 h post all three interventions	• Significant improvement in $HOMA_{IR}$ and FIRI 24 and 48 h post HyEx60 • Significant improvement in $HOMA_{IR}$ and FIRI 24 h post, but non-significant change 48 h post Hy5:5 • Non-significant change in $HOMA_{IR}$ and FIRI 24 and 48 h post Nor5:5	18
Mackenzie et al. (2012b)	T2D • Age: 57.5±2.3yr Gender andnumber: M 8 • Baseline FBG: 7.5±0.5 mM • BMI: 29.2±2.9	• Self-controlled • Single bout cycle exercise in a hypoxia room with FiO_2 0.147, follow-up at 24 h and 48 h • Interventions: 1) HyEx60: Continuous 60 min exercise at 90% lactate threshold 2) HyEx40: to complete the same total work as HyEx60 in 40 min 3) HyEx20: to complete the same total work as HyEx60 in 20 min	• Significant decrease in GLU immediately post HyEx60 and HyEx40, non-significant change post HyEx20 • Significant decrease in FBG 24 and 48 h post HyEx60 and HyEx40 • Significant decrease in FBG 24 h, but not at 48 h, post HyEx20	• Significant improvement in $HOMA_{IR}$, FIRI and QUICKI 24 and 48 h post HyEx60 and HyEx40 • Significant improvement in $HOMA_{IR}$, and FIRI 24 h, but no at 48 h, post HyEx20	18
Schreuder et al. (2014)	T2D Hypoxia group • Age: 57±6 yr Gender and number: M 9, F 1 • Baseline FBG: 7.5±2.8 mM • BMI: 30.9±4.1 Normoxia group • Age: 52±8 yr Gender and number: M 5, F 4 • Baseline FBG: 7.4±2.6 mM • BMI: 36.0±6.5	• Randomly allocated to a hypoxia or a normoxia group • Cycle exercise at 70-75% heart rate reserve, 45 min per session, 3 sessions per week, for 8 weeks • Hypoxia-training in a chamber with FiO_2 0.165, or • Normoxia-training	• No significant difference in FBGbetween and within the two groups pre and post the intervention	• No significantdifferences in HbA1c, $HOMA_{IR}$ and INS between and within the two groups pre and post the intervention	20
Gatterer et al. (2015)	Obese • Age: 50±1yr Hypoxia group • Gender and number: M 4, F12 • Baseline FBG: 123.0±41.3 mg/dl (6.83±0.23 mM) • BMI: 37.9±8.1 Normoxia group • Gender and number: M 6 F, 10 • Baseline FBG: 117.3±39.0 mg/dl (6.52±0.22 mM) • BMI: 36.3±4.2	• Randomly allocated to a hypoxia or a normoxia group • Cycle and/or treadmill exercise at 65-70% maximum heart rate, 90 min exercise and 90 min rest, 2 sessions per week, for 8 months • Assessments at 3 month and post intervention • Hypoxia-training in a chamber with FiO_2 0.122 or • Normoxia-training	• No significant difference in FBGbetween and within the two groups pre and post the intervention	• Significant decrease in BMI in the hypoxia group at 5 weeks, 3 months and post intervention • No significantdifferences in HbA1c, between and within the two groups pre and post the intervention	21

BMI: body mass index; FIRI: fasting insulin resistance index;FBG: fasting blood glucose; GLU: blood glucose; $HOMA_{IR}$: homeostasis models of insulin resistance; INS: insulin concentration; QUICKI: the quantitative insulin-sensitivity check index; T2D: type 2 diabetes

The dose-response relationship has not been established for the effects of hypoxia intervention on GLU. It appears that a hormesis phenomenon exists for the beneficial effects of hypoxia intervention. Multiple Reviews suggest that thehormetic benefits seem to be associated with hypoxia exposure lasting between 5-20 min, for sessions of 60-70 min at 80-90% SpO_2 or 0.09-0.16 FiO_2, and 1-15 episodes per day; whilst severe hypoxia (FiO_2 0.02-0.08) and more episodes per day elicit progressively greater pathology (Mateika et al., 2015; Navarrete-Opazo & Mitchell, 2014; Neubauer, 2001). The intervention protocols employed by the studies included in this review were within the range of these recommendations.

The doses of hypoxia are commonly defined by either a fixed level of FiO_2 or target level of SpO_2, with varied time ratio of hypoxia to normoxia, duration and frequency (sessions per day or per week). In the studies that utilised a hypoxia chamber for intervention on an individual or a group of participants, the dose is normally defined by the percentage of oxygen in the air (FiO_2). The FiO_2 serves as an accurate description of the environmental hypoxia, however, given the degree of individual variability in response to hypoxic stimuli, hypoxaemia would be a more appropriate indication of physiological response to hipoxia (Bassovitch & Serebrovskaya, 2009). These issues are quite relevant to consider in regards to the questions surrounding the most appropriate mode of delivery.Exposure via a hypoxicatorcould cater for biofeedback control of the dose, in whichthe $SpO_2$was closely monitored or utilised to provide feedback in controlling the hypoxia level and duration. For example, Duennwald et al. (2013) set $SpO_2$80% as the safety level, and Costalat et al. (2017) targeted SpO_2 70% for interrupting hypoxia and 95% for restarting hypoxia (Costalat et al., 2017; Duennwald et al., 2013). However, to use a hypoxicatoris resource heavy, with an intervention limited to administration to one individual at a time. Furthermore, researchers have devised a means of objectively measuring the dose of IH intervention administered, termed the 'Hypoxic Training Index' (HTi) (Bassovitch & Serebrovskaya, 2009). The HTi measures the amount of time that the arterial oxygen saturation of a patient sits within a target SpO_2 during the intervention. However, this method was not used in the studies included in this review.

Within the literature, there is substantial research that has been conducted concerning IH. Much of this deals with OSA and the associated complications and mechanisms of development for this pathology. There are varying risks and benefits that must be taken into consideration when administering a pharmaceutical treatment with a narrow therapeutic index, e.g. warfarin (Kuruvilla & Gurk-Turner, 2001), opposed to those considerably wider, e.g. naloxone(van Dorp, Yassen, & Dahan, 2007). Likewise, while benefits of IH have been seen to be associated more commonly with moderate hypoxia intensity and short duration, little has been done to establish the upper and lower limit of the hormetic effect, and hence the therapeutic index remains largely unclear. As such hypoxia is most commonly described, within medical resources, as a negative phenomenon strongly associated with metabolic syndrome and OSA (Kent, McNicholas, & Ryan, 2015). These detrimental health outcomes seem to be more commonly reported after exposure to severe levels, high frequencies and increased duration of hypoxia. Examples of these conditions are described in the literature as involving hypoxia bouts of $FiO_2$0.05-0.07, with between 25–60 bouts of exposure to hypoxia per hour, for 8–12 hours total exposure to IH (Iiyori et al., 2007; Louis & Punjabi, 2009; Polak et al., 2013; Savransky et al., 2009; Shin et al., 2014). There is also a recent report that three hours intermittent exposure to hypoxia (25 s with 5% oxygen, followed by 2 min normoxic air, 25 cycles per hour) resulted in increased blood glucose and no change in insulin sensitivity in a group of healthy adults (Newhouse et al., 2017).

There have been a small number of reports in the literature that utilised animal models of diet-induced obesity or diabetes to examine the effects of IH (simulated altitude 3000-5000m, normobaric or hypobaric hypoxia), with or without exercise, on glycose homeostasis and relevant mechanisms (X. Chen et al., 2016; Ling et al., 2008; Tian et al., 2016). These studies all reported a significant decrease of FBG after 3-5 weeks (1-8 hours per day) intervention with moderate hypoxia in obese rodents with hyperglycaemia. Benefits have been attributed to IH intervention, including reduced plasma fructosamine and increased skeletal muscle glycogen (X. Chen et al., 2016), decreased serum triglycerides, cholesterol, epididymal fat mass and body weight, along with improved hepatic steatosis, IR and oral glucose tolerance (C.-Y. Chen et al., 2010; Tian et al., 2016). Expressions of glucokinase, insulin receptor subsrate-1 (IRS-1), IRS-2 and hypoxia inducible factor 1α were also found to increase following IH intervention (Tian et al., 2016), with increased GLUT4 when administered in combination with an exercise régimen (Chiu et al., 2004). These findings are promising and underscore the need for more trials in human patients to determine the efficacy of IH in management of IFG.

To explore the underlying mechanisms for the effects of IH on IFG is beyond the scope of this systematic review. There has been conflicting evidence in the literature that exposure to hypoxia could result in development of insulin resistance, but could also improve glucose uptake (Mackenzie & Watt, 2016). Hypoxia treatment is a relatively new candidate as a potential intervention for IFG. As such, the mechanisms possibly responsible for thehormetic effect are not well established. It is known that exercise can improve glucose transport via either insulin-dependent or insulin-independent pathways, and it is speculated that muscle contraction can increase the translocation of GLUT4 vesicles through the sarcolemma via either AMPK (adenosine monophosphate-activated protein kinase) or calcium-dependent mechanisms (Santos, Ribeiro, Gaya, Appell, & Duarte, 2008). It has been proposed that hypoxia might stimulate the glucose transport and metabolism in skeletal muscle via AMPK-dependent mechanism, and not induce whole body insulin resistance (Mackenzie & Watt, 2016).

5. Conclusions

There is a paucity of investigations in the current literature that are specifically designed to evaluate the efficacy of 'rest in hypoxia' as a means of intervention for impaired glucose homeostasis. There has been a small number of reports on the acute effect of single bout exposure to moderate hypoxia, with consistent results of temporary improvements in blood glucose and insulin resistance. However, there are few investigations on the effects of repeated exposure to IH on IFG, IGT and T2D, particularly randomised controlled clinical trials.

The findings for the acute effects of hypoxia exposure in human patients, together with evidence from long-term IH intervention in animal studies, set a foundation for further investigations on the potential applications of IH as a means of treatment for IFG, as suggested in the literature. Well-designed clinical trials and empirical studies, with clear description of the dosage, preferably by physiological responses, are also needed to establish the optimal range for hormetic benefits, and the underlying mechanisms for the treatment effects. Although the IH may not replace exercise and physical activity for their benefits on cardiovascular and/or musculoskeletal systems, it has the potential as an alternative or complementary intervention for individuals with metabolic diseases but limited capacity in participating in regular exercise.

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