Glucose Homeostasis During Short-term and Prolonged Exposure to High Altitudes

Orison O. Woolcott, Marilyn Ader, and Richard N. Bergman

Diabetes and Obesity Research Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048

Most of the literature related to high altitude medicine is devoted to the short-term effects of high-altitude exposure on human physiology. However, long-term effects of living at high altitudes may be more important in relation to human disease because more than 400 million people worldwide reside above 1500 m. Interestingly, individuals living at higher altitudes have a lower fasting glycemia and better glucose tolerance compared with those who live near sea level. There is also emerging evidence of the lower prevalence of both obesity and diabetes at higher altitudes. The mechanisms underlying improved glucose control at higher altitudes remain unclear. In this review, we present the most current evidence about glucose homeostasis in residents living above 1500 m and discuss possible mechanisms that could explain the lower fasting glycemia and lower prevalence of obesity and diabetes in this population. Understanding the mechanisms that regulate and maintain the lower fasting glycemia in individuals who live at higher altitudes could lead to new therapeutics for impaired glucose homeostasis. **(*Endocrine Reviews* 36: 149–173, 2015)**

I. Introduction

Although there is abundant literature on the short-term effects of exposure to high elevations on human physiology (1–5), including observations documented more than four centuries ago (6), as well as early experimental work performed by Paul Bert in the nineteenth century (7), the impact of prolonged exposure, particularly on blood glucose regulation, has received little attention. This is surprising because approximately 7% of the world's population (ie, ~440 million people) resides above 1500 m (8), particularly since the number of people living at high elevations has been increasing considerably (by 20%) since 1990 (Figure 1). A plurality of those residing at higher elevations (>4000 m) are primarily from the Andes and Tibet (9). In some Andean countries such as Peru, the percentage of the population living at higher

ISSN Print 0163-769X ISSN Online 1945-7189
Printed in U.S.A.

Received July 30, 2014. Accepted February 6, 2015.
First Published Online February 12, 2015

Abbreviations: AMPK, AMP-activated protein kinase; BMI, body mass index; GLUT4, glucose transporter 4; GLP-1, glucagon-like peptide 1; HGO, hepatic glucose output; HIF, hypoxia-inducible factor; HOMA, homeostasis model assessment; OSA, obstructive sleep apnea.

Figure 1.

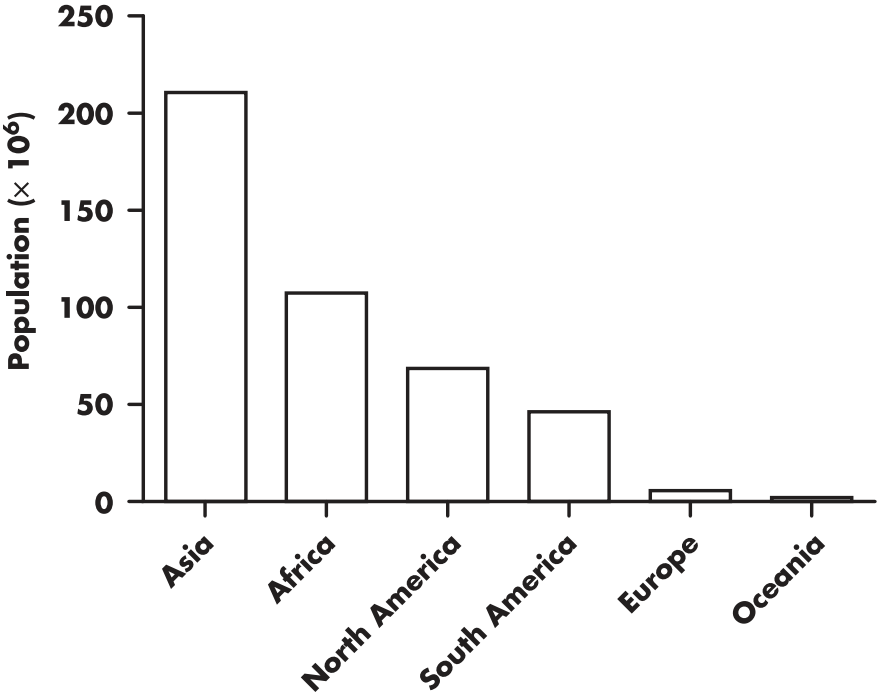

Figure 1. Number of people worldwide living above 1500 m estimated for the year 2000. Adapted from the Center for International Earth Science Information Network (8).

elevations is quite large. Approximately, 25% of Peruvian residents live above 2500 m (www.inei.gob.pe). In the United States, approximately 7.5 million people live above 1500 m (8).

Many environmental factors differ with prevailing altitude, namely: 1) the partial pressure of oxygen (PaO_2) in the breathed air; 2) ambient temperature; 3) relative humidity; and 4) solar and cosmic radiation. Even the composition of bacteria in ambient air and soil varies with altitude (10, 11). However, it is generally accepted that most physiological changes that take place in individuals exposed to high elevation are due to ambient hypoxia (ie, due to a decrease in the PaO_2), which occurs as a consequence of a low total atmospheric pressure, although the percentage of oxygen in the air remains the same (20.9%). Whether hypobaria (low atmospheric pressure) induces different physiological changes compared with those produced by hypobaric hypoxia is still in debate (12, 13).

At sea level, the PaO_2 and atmospheric pressure values are 149 and 760 mm Hg, respectively. At the top of Mount Everest (8848 m), those values are reduced by two-thirds (1). Not surprisingly, the human body activates numerous adaptive mechanisms in response to an exposure to high elevations (1, 2). Although the PaO_2 at 1500 m is approximately 80% of that at sea level (2), the arterial oxygen saturation remains within normal values (≥95%). However, initial adaptive changes become more evident above 1500 m, including increased heart rate, hyperventilation, and subsequently, increased red blood cell mass (3, 4). In healthy subjects, the inverse relationship between oxygen saturation of hemoglobin and altitude is more dramatic over 3000 m (14), which may lead to more profound adaptive mechanisms.

Additional mechanisms are involved in the human adaptation to prolonged exposure to higher altitudes (eg, individuals born and raised at low altitude that migrated to and permanently live at elevated regions). In fact, native inhabitants at altitudes above 3000 m differ in circulatory and hematological features compared with natives of lowlands. For example, children born and residing over 3000 m have a persistent right ventricular predominance compared with children born and residing below 1000 m (15). Young adult men living at 4540 m have considerably higher hemoglobin concentrations (as well as increased hematocrit) compared with men living at 150 m (16). Moreover, individuals residing at very high altitude have a larger chest circumference and cyanosis in their lips and skin (17, 18). What it is unclear is whether the environment, rather than genetic factors, mainly determines the phenotype of a high-altitude individual. These factors have been discussed elsewhere (17–20).

The purpose of the present review is to discuss the most current data about glucose homeostasis in individuals living above 1500 m. We will focus particularly on the possible mechanisms, mainly from an integrative (systemic) point of view, that could explain the lower fasting glycemia and lower prevalence of obesity and diabetes in humans at higher altitudes. In addition, we will briefly discuss the studies examining the effects of simulated altitude (hypobaric hypoxia simulated in a decompression chamber) and experimental hypoxia alone on glucose homeostasis because information on these topics is more limited. Cited references were mainly obtained from PubMed, in either the English or Spanish language.

In this review, we considered three altitude environments, as suggested by the International Society for Mountain Medicine (www.ismm.org). High altitude was defined as ≥1500 m and below 3500 m; very high altitude, ≥3500 m and below 5500 m; and extreme altitude, ≥5500

m. Because there is no consensus on the definition of acute and chronic exposure, we arbitrarily defined very acute exposure when the exposure duration is less than 60 minutes; acute exposure, when it lasts 1–24 hours; subacute exposure, when it lasts between 1 day and less than 3 months; and chronic exposure, when it lasts ≥ 3 months. However, for the purposes of this review, very short and acute exposures are considered short-term effects, whereas subacute and chronic are considered long-term effects.

II. Short-term Effects of Altitude on Glycemia

Fasting glycemia of healthy lowlanders exposed to very high altitude has been reported to increase (21–23), decrease (24), or remain unchanged (25, 26). Divergent results may be due to period of exposure. In fact, exposure to very high altitude causes an increase in fasting glycemia in the initial 2–3 days (21–23). This initial increase in glycemia is attenuated as the exposure persists for more than 1 week (25, 26) and may even decrease below pre-exposure values in the second week of a stay at very high altitude (24). Thus, acclimatization to high elevations may allow normalization of glycemia after initial transient hyperglycemia.

Certainly, other factors may also explain the discrepancies reported in regard to the effect of altitude exposure on fasting glycemia. Physical activity appears to contribute to the susceptibility to hyperglycemia during short-term exposures to high altitude. Exposure to very high altitude induces hyperglycemia in healthy individuals under non-resting conditions (21, 22), but the same exposure does not affect glycemia in individuals remaining at resting conditions (27, 28). One explanation is that physical work could lead to increased sympathetic activity, resulting in hyperglycemia. Numerous studies examining the effect of altitude exposure on urine or plasma catecholamines have reported an increase in catecholamines, mainly norepinephrine, as reviewed by Rostrup (29) and Richalet (30). However, elevation in catecholamines does not always occur after altitude exposure (29), suggesting that altitude-induced hyperglycemia may not be fully explained by catecholamines. Elevation of cortisol during short-term exposure to high altitude (31) could also contribute, at least in part, to the transient hyperglycemia. There is a possibility that prevailing fasting conditions could also mediate the hyperglycemic response after altitude exposure. For example, decreased glycemia has been observed after acute exposure to hypobaric hypoxia in nondiabetic subjects (Figure 2) while remaining in prolonged fasting states (O. Woolcott, unpublished data).

The previous findings suggest that hyperglycemia may develop in the initial days after exposure to high altitudes, probably secondary to increased stress-related hormones, namely cortisol and norepinephrine. However, it is remarkable that prolonged exposure to high altitudes may instead have potential benefits on glucose homeostasis. Indeed, numerous studies conducted in individuals exposed to high or very high altitude from 10–90 days have not reported hyperglycemia (23, 24, 26, 28, 32–35), regardless of whether they were exposed to simulated (hypobaria and hypoxia) or natural altitude. Moreover, some of these studies show evidence that prolonged exposure to altitude may lower glycemia (24, 28, 32). Figure 3 depicts the different fasting glycemia variations in response to short and prolonged exposure to high altitudes in humans. In fact, acclimatization to high altitude appears to increase the fuel dependence on blood glucose not only in the human skeletal muscle (28, 36, 37) but also in the heart muscle (38). This mechanism may offer a more efficient fuel me-

Figure 2.

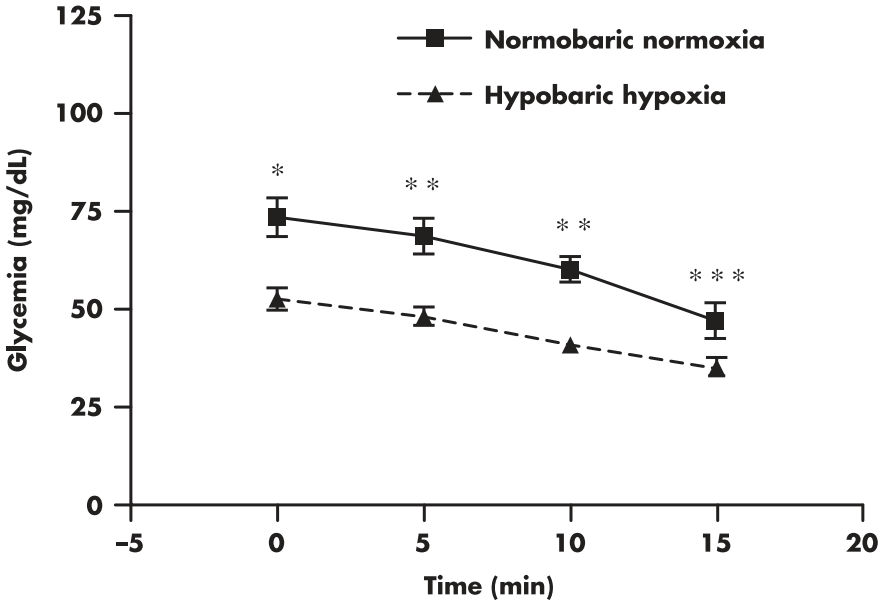

Figure 2. Glycemia profile during an iv insulin tolerance test performed at 150 m (normobaric normoxia) and after acute exposure to simulated altitude (hypobaric hypoxia) at 3200 m. Male subjects (BMI, 26 ± 3.53 kg/m^2 [mean ± SD]) were in an approximately 15-hour fasting state before the commencement of the test (O. Woolcott, unpublished data). *, $P < .01$; **, $P < .001$; ***, $P < .05$, hypobaric hypoxia vs normobaric normoxia.

Figure 3.

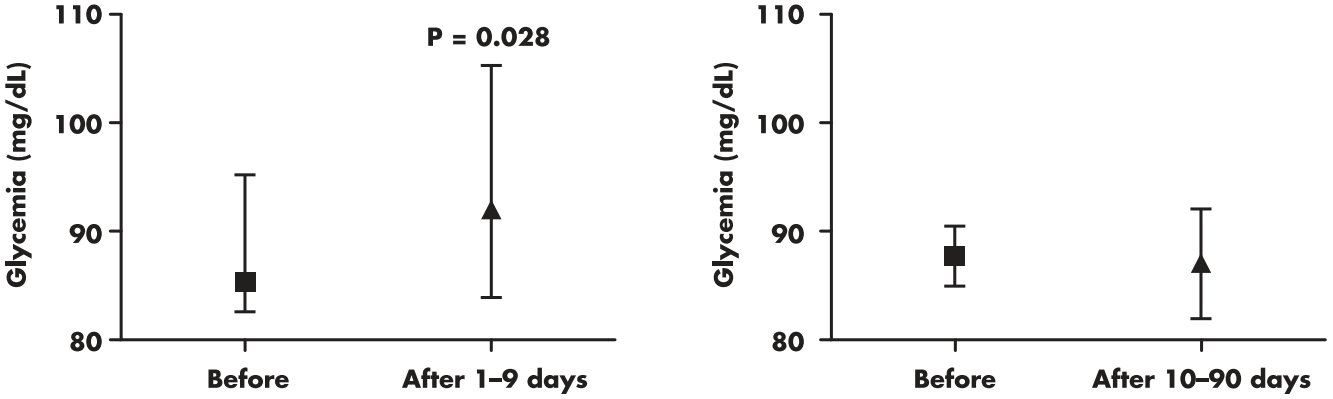

Figure 3. Differences in fasting venous glycemia in response to short and prolonged exposure to high altitudes in nondiabetic humans. Plots were created by using reported glycemia values from studies conducted in lowlanders exposed for short (1–9 d) (21, 22, 24, 25, 27, 28, 264–266) and prolonged (10–90 d) (23, 24, 26, 28, 32–35) periods to high altitude and very high altitude, under simulated (hypobaria and hypoxia) or natural conditions. Columns and bars are medians and interquartile ranges, respectively.

tabolism (of glucose) in response to hypoxia, as compared with fatty acid oxidation (39).

III. Glycemia and Insulinemia Among Highlanders

There is compelling evidence for lower fasting glycemia in clinically healthy residents living between 3000 and 4500 m, compared with residents living below 500 m. This difference has been reported in men (40–44), nonpregnant women (45–47), pregnant women (47, 48), nondiabetic subjects (40, 45, 48), and also in neonates (48) and appears to be independent of body mass index (BMI) (40, 45, 48). Likewise, individuals living at 3200 m have been shown to have lower 12-hour blood glucose profiles compared with individuals living near sea level (40). From available data (38, 41–43, 49), we have estimated a median fasting plasma glucose concentration of 81.6 mg/dL (interquartile range, 72.2–81.8 mg/dL) for adult males living above 3000 m, whereas in residents from low altitude the estimated value was 91.2 mg/dL (81.9–95.4 mg/dL). In nonpregnant adult females, the median fasting plasma glucose was estimated to be 71.7 mg/dL (68.4–88.7 mg/dL) and 85.9 mg/dL (82.8–93.8 mg/dL), for residents living above 3000 m and those from low altitude, respectively (45–47).

Additional compelling evidence of lower fasting glycemia at higher altitudes comes from a large clinical study conducted in a nationally representative sample from Peru, including adult subjects of both sexes, with or without diabetes (50). This study showed an inverse association between fasting glycemia and altitude: 85 ± 26.6 mg/dL (mean ± SD) at < 1000 m (n = 2425); 83 ± 14.4 mg/dL between 1000–2999 m (n = 808); and 78.8 ± 17.9 mg/dL at > 3000 m (n = 959). It is important to note that although populations from these three altitude bands had comparable mean age, BMI was significantly lower at higher altitudes. However, as pointed out before, independent studies have shown lower glycemia at high altitudes in BMI-matched individuals (40, 45, 48). Nevertheless, it is unclear whether the lower glycemia at higher altitudes reported among Peruvian adult individuals could be explained by differences in diet, physical activity, or family history of diabetes mellitus.

The preponderance of the evidence supports better glycemic control at higher altitudes. However, a few studies have reported no significant differences in fasting glycemia between lowlanders and highlanders (26, 38, 49, 51, 52), although a trend for a lower glycemia at higher altitudes was observed in most of these studies (38, 49, 51, 52). One should note that virtually all studies showing lower glycemia at higher altitudes have been conducted in Andean populations. Therefore, further studies are needed to determine whether differences in glycemia exist between lowlanders and highlanders from other regions of the world. For example, no association between fasting glycemia and altitude has been reported among Indian individuals (26). In that regard, there is good evidence that there are some genetic differences, for example between Andeans and Tibetans (53, 54), including those in pathways known to affect glucose metabolism (55).

A. How reliable are the measurements of plasma glucose at high altitudes?

It has been argued that the lower reported glucose levels observed at higher altitudes are the result of methodological

artifacts. There is strong evidence demonstrating the inconsistency of the performance of portable blood glucose meters in the presence of low oxygen tension (56–61) and low ambient temperatures (56, 62). Even glucose-dehydrogenase-based glucose meters, which have been shown to be more accurate at high altitudes (57, 63, 64) due to the insensitivity of glucose dehydrogenase to changes in O_2 tension (65, 66), are still prone to error in low ambient temperatures (56). In addition, an increased number of red blood cells may also affect glucose readings in blood glucose meters (67, 68), due to mechanical impairment of the diffusion of plasma into the reagent membrane (69).

Another potential artifact is an accelerated ex vivo glycolysis (70, 71). Elevated red or white blood cell mass, independent of altitude, may result in pseudohypoglycemia (70, 71). This has also been demonstrated in individuals living at high altitudes (72), explaining the substantial differences in measured glucose concentrations in plasma vs whole blood from the same individual (41, 43) (Figure 4).

For the reasons explained before, glucose measurements in plasma samples are strongly recommended (73, 74). Studies comparing fasting glycemia between low and high-altitude populations have used different methodologies (Somogyi-Nelson, Folin-Malmros, Saifer-Gerstenfeld, glucose-oxidase based method, and hexokinase-glucose-6-phosphate dehydrogenase-coupled enzyme assay) (40–45, 48, 75), including methods that are potentially prone to error due to hypoxia, cold temperature, and erythrocytosis (increased red blood cell mass). Almost all of these studies have shown a lower glycemia at higher altitudes. However, the lower fasting glycemia in individuals living at higher altitudes has been confirmed in plasma samples (41, 42, 45, 46, 48, 75, 76). Moreover, these differences have also been found in plasma samples collected at low and high altitudes and later analyzed at sea level (45). Thus, there is little doubt that fasting glycemia is lower at high altitudes. The question that remains is why?

B. Does insulin explain the lower glycemia in highlanders?

Because blood glucose levels are tightly regulated by insulin, it is possible that the lower glycemia among highlanders may be explained by higher plasma insulin concentrations. Lower (45, 47, 48), similar (40, 41), or higher fasting plasma insulin (26) has been reported in highlanders as compared with lowlanders. However, age- and BMI-matched studies do not support hyperinsulinemia as a cause of the lower glycemia (40, 45). Moreover, similar fasting plasma levels of C-peptide, a marker of insulin release (77, 78), and lower plasma insulin levels have been reported in nonpregnant women from high altitude as compared with lowlanders, despite higher BMI (47), suggesting higher hepatic insulin extraction in female highlanders. It is unlikely that the discrepancies on insulin differences between lowlanders and highlanders among studies were explained by the assay method because RIA was used in most of the studies (26, 40, 41, 45, 47).

Figure 4.

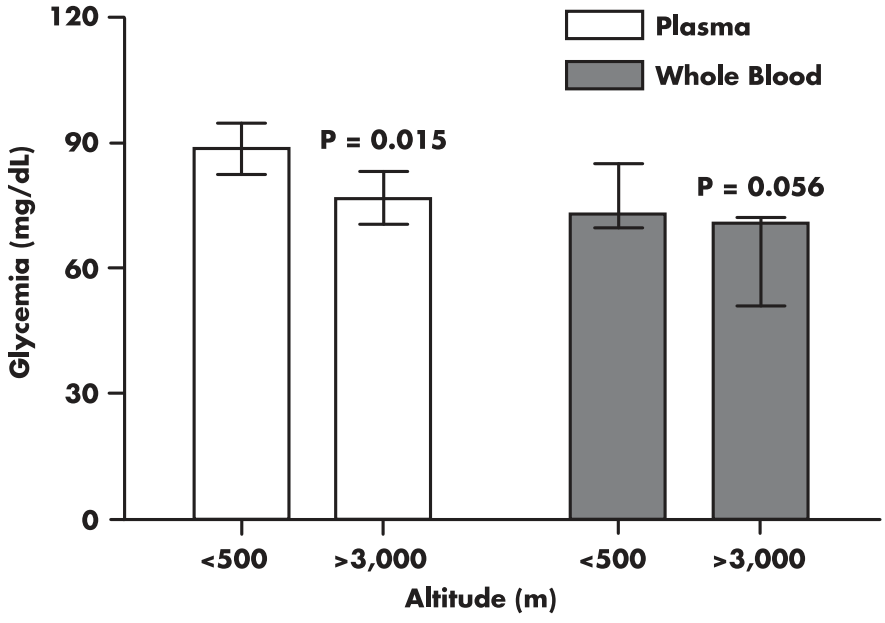

Figure 4. Differences in fasting venous glycemia from humans living at low altitudes compared with those living at high altitudes. Figure was generated using reported values from studies that measured plasma glucose (38, 41–43, 45, 46, 75) and whole-blood glucose (26, 40, 41, 43, 123). Columns and bars are medians and interquartile ranges, respectively.

C. Is the lower glycemia at higher altitudes acquired?

Although numerous studies support the hypothesis that individuals who live at higher altitudes have lower fasting glycemia, little is known as to whether this phenomenon also occurs in individuals who are natives of sea level areas but migrated to or permanently live at high altitudes. There are some studies that support the idea that lower fasting glycemia may be an acquired trait. Lowlanders exposed to very high and extreme altitude for 3–8 weeks showed a significant reduction in fasting glycemia (79, 80). Similar findings have been reported in lowlanders chronically exposed to very

high altitude for 24 months, independent of physical activity (44). Whether a decrease in glycemia can be attained in a relatively short time in the general population at moderate altitudes could have potential implications for treating diabetes.

The benefit of living at high altitudes on glucose metabolism appears to dissipate with migration to sea level. These observations were first reported by Carlos Monge-Cassinelli, who found similar fasting glycemia between natives of the coast living at sea level and natives of the Andes who were residing at sea level for at least 1 year (81). Another study reported that highlanders who lived for 2 years at sea level had glycemia similar to native residents of sea level (43). Collectively, these studies indicate that prolonged exposure to high altitude may lower glycemia in lowlanders, whereas highlanders may increase their glycemia when moving to low altitude, suggesting an acquired process.

IV. Endogenous Glucose Production at High Altitude: Role of the Liver

The mechanism(s) that may explain the lower fasting glycemia at higher altitudes is little understood. In the postprandial state, blood glucose concentration depends on glucose entry into the bloodstream from diet and endogenous sources, primarily the liver, and also depends on peripheral glucose disposal (glucose uptake), primarily by the skeletal muscle (82). However, in the fasting state, blood glucose is supplied primarily by the liver (80%) and to a lesser extent by the kidney (20%) (83), with uptake by the central nervous system. Therefore, it is possible that the lower fasting glycemia among highlanders could be determined by a lower glucose production in the liver.

A. Hepatic glucose output (HGO) in lowlanders exposed to high altitude

The widely accepted method to assess HGO is the isotope dilution method (84, 85). To date, no study has assessed HGO in individuals permanently living at high altitude. Intravenous [6,6-^{2}D]glucose infusion experiments in male lowlanders have shown that acute exposure to very high altitude increases HGO, as measured by the rate of glucose appearance, compared with pre-exposure values (1.99 ± 0.11 vs 1.47 ± 0.19 mg·kg^{-1}·min^{-1}, respectively) (86). Conversely, after 7 days of exposure to very high altitude, HGO was similar to pre-exposure values (21), as assessed by the euglycemic hyperinsulinemic clamp technique (87). In both studies, HGO was associated with plasma epinephrine concentrations (21, 86). These results further support the idea that short-term exposure to very high altitude causes a transient hyperglycemia (in which sympathetic activation is likely to be involved) that is attenuated as the exposure continues. However, the question remains as to whether individuals permanently living at high altitudes have lower HGO compared with lowlanders.

B. Role of glucagon among highlanders

HGO regulation is complex, and it involves a close feedback among glucagon, nonesterified fatty acids, insulin (88), and neural input (89). Glucagon, fatty acids, and catecholamines stimulate HGO (90), whereas insulin suppresses HGO (91–93). Studies performed on highlanders using the iv glucagon tolerance test have shown a lower hyperglycemic response to glucagon as compared with lowlanders (94, 95). This may be due to lower endogenous glucose production, primarily the HGO, rather than renal glucose output, because the latter is not affected by glucagon (96, 97) Nevertheless, a major limitation in the interpretation of the iv glucagon tolerance test is that endogenous insulin release will occur as a compensation of the glucagon-induced hyperglycemia (98), unless insulin is experimentally suppressed. Therefore, this approach may confound the contribution of the liver due to concomitant insulin-mediated glucose uptake in the skeletal muscle.

An intriguing finding is lower fasting glycemia and higher fasting glucagonemia in healthy natives from the Andes compared with Australian Caucasians (23), raising the possibility that highlanders could have lower hepatic glucagon sensitivity, which could result in lower HGO.

C. Role of hepatic glycogen content

Studies in rodents chronically exposed (3–8 mo) to natural and simulated very high altitude have shown a considerable reduction (by ~50%) in hepatic but not muscle glycogen content (99–101), probably as a consequence of reduced activity of gluconeogenic enzymes (100). In fact, the decrease in hepatic glycogen content was accompanied by a significant reduction in glycemia (99). Moreover, HGO is directly related to liver glycogen content in humans (102) and rats (103), suggesting that liver glycogen could contribute to the lower blood glucose among highlanders. However, it cannot be ruled out that low blood glucose may cause a decrease in liver glycogen content. Further studies are needed to elucidate the contribution of the liver to glucose regulation among highlanders.

V. Effect of Altitude and Hypoxia on the Skeletal Muscle

Because fasting plasma glucose levels are determined by a balance between HGO (primarily) and whole-body glu-

cose disposal, the possibility that a higher glucose disposal contributes to the lower fasting glycemia in highlanders has to be considered. In fact, in the fasting state, the noninsulin-mediated glucose disposal accounts for approximately 70–75% of the whole-body glucose disposal in humans (104, 105). Although no study has quantitatively estimated the noninsulin-mediated glucose disposal or the insulin-mediated glucose disposal (insulin sensitivity) in highlanders, there is evidence supporting a higher whole-body glucose disposal in residents of high altitudes.

A. Short-term effects of altitude and hypoxia in vivo

1. Effect of altitude on glucose disposal in lowlanders

Although some human studies have shown improved oral glucose tolerance after exposure to high altitude (106, 107), such findings do not unequivocally indicate a higher glucose disposal because glucose profile changes during oral glucose tolerance test are affected by many factors, including gastrointestinal motility, rate of glucose absorption (108, 109), and incretin hormones (110, 111). In fact, experiments with isotope-labeled glucose have shown a decrease in the rate of glucose disappearance after 2- to 10-day exposure to very high altitude (21, 32). Conversely, more prolonged exposure to very high altitude appears to increase glucose disposal (28). These findings are also consistent with the studies showing a transient hyperglycemia in the lowlander exposed short term to high altitudes.

2. Effect of hypoxia on insulin sensitivity in lowlanders

Because hypoxia is a key factor associated with altitude, examining the short-term effect of hypoxia on insulin sensitivity in vivo may help to explain the glucose regulation in the highlander. Studies in healthy individuals (112, 113) were designed to substantially reduce peripheral oxygen saturation (≤85%) by administration of hypoxic air (~5% O_2). The latter studies showed a decrease in insulin sensitivity as assessed by the glucose infusion rate during euglycemic hyperinsulinemic clamp (87), the "gold standard" method, and the mathematically based "minimal model" (114). Conversely, mild hypoxia (13–15% O_2) improved insulin sensitivity in type 2 diabetic subjects (~2.3×10^{-4}/min [mU/L] and ~1.4×10^{-4}/min [mU/L], hypoxia and normoxia, respectively) as assessed by the minimal model (115). Likewise, mild hypoxia has been shown to increase glucose infusion rate by approximately 20% (from ~8.3 to 9.2 mg/kg/min) in obese subjects (116). Moreover, mild hypoxia (13% O_2) has been shown to decrease glycemia in type 2 diabetic subjects (117). These findings suggest that severe hypoxia, associated with a dramatic reduction in peripheral oxygen saturation, may impair insulin sensitivity, whereas mild hypoxia, which is associated with a more moderate reduction in peripheral oxygen saturation, may improve insulin sensitivity.

3. Effect of hypoxia on insulin sensitivity in animals

A study conducted in mice breathing hypoxic air (10% O_2) for 4 weeks showed an increase in insulin sensitivity, concomitant with a significant reduction in fasting glycemia (118). Likewise, dogs breathing 8% O_2 had an increased rate of whole-body glucose disappearance and leg glucose uptake, although fasting glycemia did not change (119). In addition, perfusion experiments in rat hind limb under anoxic conditions have also shown higher glucose uptake (120, 121). Together, these studies further support an important beneficial effect of prolonged hypoxia on insulin sensitivity. However, the dissociation is still unclear between the changes in insulin sensitivity and the fasting glycemia after acute exposure to hypoxia.

B. Prolonged effects of altitude: evidence in highlanders

Although the evidence presented so far clearly shows that short-term exposure to high altitude and hypoxia may improve glucose disposal in the lowlander, this does not prove a higher glucose disposal in the highlander.

1. Intravenous glucose tolerance

Emilio Picón-Reátegui was one of the pioneer researchers who systematically studied glucose metabolism in Andean residents of very high altitude. One of his most important contributions was to demonstrate a higher glucose disposal in the highlander (122). Male subjects residing at 4540 m showed a more rapid decline of glycemia during the iv glucose tolerance test as compared with lowlanders (122). Although the quantity of glucose administered was not corrected for body weight, reanalysis of available data from this study (122) shows that the differences in glucose profile remained significant when groups were matched for BMI (Figure 5). Using the same test, other investigators have confirmed the previous findings in males and females (42, 46).

2. Oral glucose tolerance

Studies in Andean and Indian healthy populations living at very high altitude have shown that these individuals have a better oral glucose tolerance compared with their fellow citizens living at low altitude (44, 123). Among obese individuals, it appears that highlanders living at 3200 m also have a better oral glucose tolerance as compared with sea-level residents (49), although it is not clear whether these differences are explained by differences in BMI between groups. Nevertheless, these findings confirm

Figure 5.

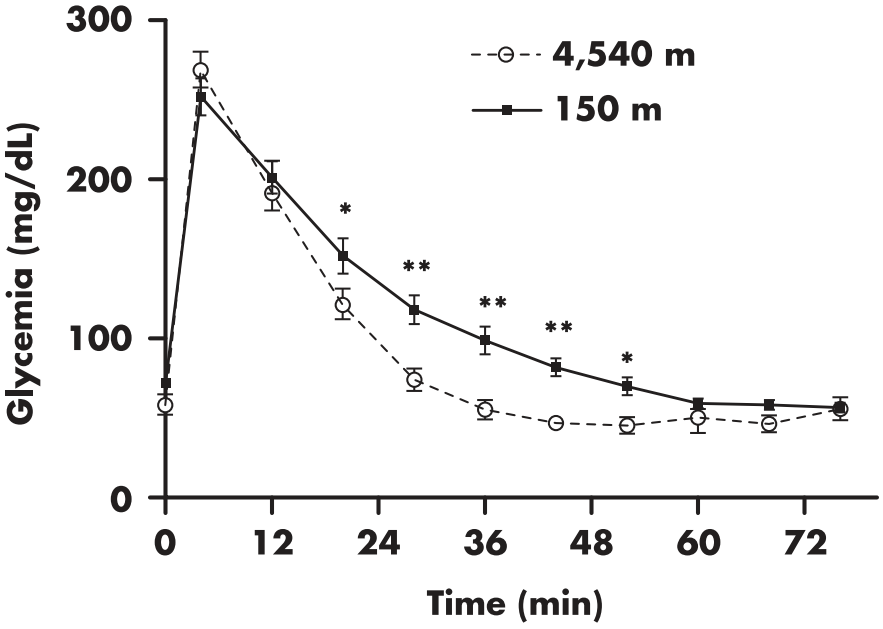

Figure 5. Intravenous glucose tolerance test in subjects residing at 4540 m (n = 7) and subjects residing at 150 m (n = 8) above sea level. Figure was created using available data from Ref. 122, including only subjects with lean BMI (<25 kg/m^2). Note the pronounced and faster decrease of glycemia in the higher altitude group after glucose administration (at min 0). Symbols and bars represent mean and SE values, respectively. *, $P < .05$; **, $P < .01$.

the results from studies using the iv glucose tolerance test in highlanders.

3. Arterial-venous glucose difference

The difference in arterialized venous-venous (peripheral) glucose concentration, which is proportional to the rate of glucose disposal assessed by tracer-labeled glucose (124), has been reported to be greater in men and pregnant women living at high elevations as compared with lowlanders (48, 123), indicating that highlanders have a higher rate of glucose disposal in peripheral tissues than the rate of endogenous glucose output.

4. Insulin tolerance

Residents of very high altitude appear to have a more sluggish return of glycemia to baseline from 60 to 120 minutes after iv insulin administration during the insulin tolerance test, as compared with lowlanders (125). The major problem in the assessment of whole-body insulin sensitivity with this test (126, 127) is that prolonged hypoglycemia may lead to a counter-regulatory response, confounding the effect of insulin (128).

5. Homeostasis model assessment (HOMA)

A higher insulin sensitivity has been reported in women residing at very high altitude, as compared with lowlanders (45, 47), using the HOMA index (129), a surrogate measure of insulin sensitivity. However, because calculations are based on fasting blood insulin and glucose, the HOMA index could give inaccurate estimations of insulin sensitivity when fasting glycemia is very low (130). Thus, HOMA estimations in high altitude populations should be interpreted with caution.

6. Glucose uptake assessed by positron emission tomography

Noninvasive methods are also useful tools to assess glucose uptake in the human body (131). Regional myocardial uptake of 18F-labeled 2-fluoro-2-deoxy-D-glucose measured by positron emission tomography revealed a higher uptake in Quechua subjects living above 3000 m compared with lowlanders (38). Using the advantages of this technique may help to determine whether specific differences in glucose uptake exist in skeletal muscle, adipose tissue, or the liver between lowlanders and highlanders.

C. Effects of anoxia and hypoxia on glucose uptake in vitro

Previously, we have discussed the evidence in vivo of higher glucose disposal and increased insulin sensitivity in response to high altitude and mild hypoxia (28, 115, 116). In this section, we will discuss additional supporting evidence from in vitro studies in rodent and human skeletal muscle. We will not discuss the mechanisms by which altitude and hypoxia affect glucose metabolism because this topic has been extensively reviewed elsewhere (132–135). However, it should be mentioned that hypoxia favors the rate of glycolysis (132, 134, 136, 137), which may contribute to the elevation of plasma lactate levels seen in individuals exposed to high altitude (138–140). Nevertheless, whether glucose enters the glycolytic pathway or is oxidized to generate ATP, a higher glucose uptake may contribute to the lower glycemia at high altitude.

1. Glucose uptake under anoxia conditions in vitro

Philip Randle was one of the pioneers who examined the role of oxygen tension on mammal cell glucose uptake. His work on rat diaphragm muscle led to the conclusion

that anaerobic conditions increase cell glucose uptake (141). These findings were confirmed by Randle and colleagues (142) and by Wheeler (143) in the heart muscle from rats. Later, numerous studies have also reported increased glucose uptake in response to very acute exposure to anoxic conditions (gas mixture, 95% N_2/5% CO_2/0% O_2) in the skeletal muscle of rodents (144–149). Notably, the enhanced glucose uptake induced by anoxia has also been reported in the human skeletal muscle from lean and obese subjects (150) and nonobese type 2 diabetic subjects (151). Moreover, the effects of anoxia on glucose uptake in human and rat skeletal muscle have been shown to be additive to that of insulin (144, 150), but not contractile activity, suggesting that anoxia and contractile activity may stimulate glucose uptake via similar mechanisms (152).

2. Glucose uptake under hypoxia conditions in vitro

Although it is clear that anoxia stimulates glucose uptake in vitro (141–151), few studies have addressed the effect of hypoxia (more clinically relevant) on glucose uptake in the skeletal muscle.

To determine the effect of hypoxia on glucose uptake in vitro, experimental studies have exposed the whole organism to hypoxic air. For example, mice exposed to normobaric hypoxia (10% O_2) for 4 weeks showed increased soleus glucose uptake in vitro, but only in the presence of insulin (153), suggesting that hypoxia alone may not be sufficient to promote peripheral glucose uptake. In humans, hypoxic air (~15% O_2) for 10 nights resulted in increased insulin-independent glucose uptake in skeletal muscle (116). Conversely, very short exposure (~10–22 min) to hypoxic air (11.4–14% O_2) did not have an effect on human skeletal muscle glucose uptake (154), including intracellular glucose content (155), suggesting that the effect of hypoxia on glucose uptake is time dependent.

3. Effects of anoxia and hypoxia on glucose transporter 4 (GLUT4) translocation and AMP-activated protein kinase (AMPK) activity

The possible mechanisms by which anoxia/hypoxia may stimulate glucose uptake have been reviewed elsewhere (156, 157). However, it is important to point out that the GLUT4 plays a major role in insulin-dependent muscle glucose transport when translocated from intracellular pools to plasma membrane (158). Increased GLUT4 translocation and protein content of GLUT4 are also likely the main mechanisms by which anoxia stimulates glucose uptake in rodent skeletal muscle and cardiomyocytes (143–145, 159, 160). An increased GLUT4 protein content in human skeletal muscle in response to anoxia has also been reported in human skeletal muscle (151).

Skeletal muscle from rats breathing hypoxic air (9–14% O_2) for 4 weeks also showed increased GLUT4 protein content (161). These findings, however, do not answer the question as to whether hypoxia per se has a direct effect on GLUT4 content because many other possible in vivo effects may be activated or inhibited when animals breathe hypoxic air. For example, epinephrine has been shown to stimulate GLUT4 translocation in the absence of insulin (162).

Augmented AMPK activity in the skeletal muscle stimulates glucose transport (157). Recent evidence suggests that hypoxia/anoxia-induced glucose uptake is exclusively coupled to the AMPK-dependent pathway (157, 163), in contrast to muscle contraction, which activates both AMPK-dependent and AMPK-independent pathways (144, 150, 152), challenging the initial concept that anoxia and muscle contraction stimulate glucose uptake under the same mechanism.

In summary, there is strong evidence suggesting that anoxia stimulates glucose uptake by promoting GLUT4 translocation via AMPK-dependent pathway. However, little is known about the direct effect of hypoxia on glucose uptake and the possible mechanisms involved. Moreover, whether GLUT4 and the AMPK pathway contribute to the greater glucose disposal in residents of high altitudes remains unknown.

VI. Role of the Gastrointestinal Tract

Although intestinal carbohydrate absorption in humans may decrease at altitudes over 5700 m (164, 165), this threshold is too high to explain the better oral glucose tolerance in residents living at altitudes below 5000 m (44, 123). Moreover, if exposure to very high altitude causes important intestinal malabsorption, then alteration in the absorption of other nutrients should be expected. However, studies have found no evidence of protein or fat malabsorption in humans exposed to altitudes below 5000 m (166–168).

The evidence to support a possible contribution of gut hormones to the better oral glucose tolerance is limited. In fact, gut hormones have been studied only under short-term exposure to high altitudes. In nonobese individuals passively exposed to high elevations for short periods, fasting plasma ghrelin and cholecystokinin have been shown to decrease below baseline values (169–171), most likely contributing to the transient loss of appetite, a very common symptom seen during short-term altitude exposures. In contrast, plasma levels of peptide YY, an anorex-

igenic hormone, does not appear to be involved in the anorexic effect of altitude exposure (170, 172). Glucagon-like peptide 1 (GLP-1) and ghrelin are of particular interest because these hormones have opposite effects on insulin secretion and food intake. GLP-1 enhances insulin secretion and suppresses appetite (173, 174). Human studies have shown that plasma fasting GLP-1 levels are not altered after exposure to hypoxia or simulated very high altitude (175, 176), suggesting that the increased oral glucose tolerance in lowlanders after altitude exposure (106, 107) may not be related to incretin effects. Future studies are required to elucidate the mechanisms involved in the greater oral glucose tolerance among highlanders.

VII. Role of the Adipose Tissue

The breakdown of stored lipids in adipose tissue results in the release of fatty acids into the bloodstream. Elevated fatty acid levels may stimulate gluconeogenesis and glycogenolysis, resulting in fasting hyperglycemia (177). Thus, it is possible that the lower fasting glycemia may be explained by lower fatty acids levels. However, studies have reported higher (41), lower (38), or similar (22, 178) plasma fatty acid levels in highlanders as compared with lowlanders. These discrepancies among studies are probably explained by differences in methodology. Fatty acid values are highly influenced by BMI, the type of diet, fasting duration, and lipolysis ex vivo (179–182), and much of this latter information is not described. Careful studies are required to determine whether highlanders have lower fatty acid levels.

Although the adipose tissue secretes numerous hormones (183), of which adiponectin has been strongly associated with improved systemic insulin sensitivity (184), this hormone has not been studied in the highlander. However, it is interesting that adiponectin is increased after subacute exposure to very high altitude (185, 186).

VIII. Possible Link Between Hypoxia-Inducible Factor (HIF) and Glucose Homeostasis

Numerous studies have shown that living above 1500 m may have beneficial effects on glucose homeostasis. However, the mechanisms by which altitude per se signals the cascade of cellular events to produce such physiological effects are little understood. In previous sections, we have discussed studies examining the isolated effect of hypoxia on insulin sensitivity, glucose disposal in vivo (112, 113, 115–119, 154), and muscle glucose uptake in vitro (116, 153), but a direct proof that hypoxia mediates the effects of altitude on glucose homeostasis is still missing.

A. Genetic adaptation of highlanders to hypoxia

Data from genetic studies support the hypothesis that hypoxia could mediate, at least in part, the effects of altitude on human physiology, including glucose homeostasis. Some alleles of genes related to hypoxia have a higher prevalence among highlanders as compared with lowlanders (187, 188). At the cellular level, hypoxia inhibits oxidative phosphorylation and stimulates oxygen signaling pathway through the HIF-1α (156). HIF is a DNA-binding transcription factor associated with specific nuclear cofactors and exists as three isoforms in humans: HIF-1α, HIF-2α, and HIF-3α. Under hypoxic conditions, HIF-1 regulates the expression of several genes that mediate adaptive responses to low oxygen tension in different tissues. Whereas HIF-1α is widely expressed in the body, HIF-2α expression is limited to fewer tissues. However, HIF-2α may be equally essential in the regulation of the hypoxia response (189–192).

It is noteworthy that a higher frequency of a single-nucleotide polymorphism at *EPAS1* gene (HIF-2α) has been reported among Tibetans from China living above 4300 m as compared with Beijing residents living below 2000 m (87 and 9% frequency, respectively) (187). Similar increased frequency of single-nucleotide polymorphisms related to the HIF pathway (*PPARA*) has also been reported in Ethiopian residents at 3200 m compared with Ethiopians living at low altitude (188), suggesting that high altitude populations, regardless of their ethnicity, may display a genetic adaptation to hypoxia via the HIF pathway.

Interestingly, HIF-1α expression has been found to be 60% down-regulated in the skeletal muscle of Tibetan residents of very-high altitude regions as compared with Nepali lowlanders (193). Likewise, genes involved in the glycolytic pathway were down-regulated (193), suggesting a negative feedback mechanism in conditions of chronic exposure to hypoxia. In fact, chronic hypoxia exposure may result in an adaptive (evolutionary) mechanism that could be associated with the "altitude phenotype" in these populations. However, the persistent stimulus (hypoxia) may down-regulate typical responses to hypoxia as a protective mechanism. This phenomenon has been consistently observed in sea-level residents acclimated to high altitude, where the initial hyper-response in pulmonary ventilation and blood lactate accumulation after altitude exposure is followed by a more attenuated response in magnitude if the stimulus continues, as reviewed elsewhere (2, 194, 195). Another possible explanation is that high altitude residents may have increased

sensitivity to chronic hypoxia in the skeletal muscle; therefore, increased expression of genes related to hypoxia may not be needed. Further discussion related to the changes over time in gene and protein expression in response to exposure to hypoxia or altitude has been published elsewhere (196–199). Whether hypoxia is the major determinant of the genetic adaptation to high altitude remains to be explored. We believe that hypobaria (low atmospheric pressure) must also play an important role in the genetic adaptation to high altitudes because many functions in the human body are regulated via baroreceptors (200).

B. HIF and glucose uptake: evidence in vitro

Data from in vitro studies may also provide some clues as how hypoxia may mediate the effects of altitude on glucose homeostasis in the highlander. Hypoxia (14.5% O_2) increases both HIF-1α and GLUT4 mRNA expression in the human skeletal muscle (201). Moreover, muscle contraction may induce transcriptional activation of SLC2A4 (the gene encoding the protein GLUT4) together with increased expression of HIF-1α in rat skeletal muscle (202). Furthermore, a recent study in skeletal muscle clonal cells has shown that HIF-1α is involved in the regulation of glucose metabolism stimulated by insulin. Knockdown of HIF-1α expression in these cells resulted in a defect in insulin-stimulated glucose uptake due to impaired GLUT4 translocation (203). Together, these findings suggest that HIF may not only signal the effect of hypoxia on glucose uptake but also that HIF may be a constitutive element in the cell signaling of glucose uptake in normoxic conditions. This concept is supported by the findings from a study in individuals with Chuvash polycythemia (204), a congenital disorder manifested by an abnormal elevation in the number of red blood cells secondary to elevated expression of HIF genes due to a mutation in the von Hippel-Lindau gene. These individuals, despite residing at sea level, have lower blood glucose levels and glycated hemoglobin A1c (204).

IX. Diabetes and Obesity at High Altitudes

Type 2 diabetes results from an inadequate regulation of glucose homeostasis. Interestingly, there is growing evidence of a lower prevalence of diabetes at higher altitudes (50, 205–208). Likewise, obesity, a well-established risk factor for type 2 diabetes (209, 210), is less prevalent in populations from high altitudes (211). In this section we will discuss whether the lower prevalence of diabetes and obesity at higher altitudes is independent of potential confounders. In addition, we will argue about the possible explanations for this association.

A. Association between obesity and altitude

1. Obesity in adults

Independent studies have shown an inverse relationship between altitude and prevalence of obesity in representative adult populations from the Andes and Tibet (50, 207, 212, 213). Moreover, a retrospective study has concluded that individuals stationed at higher altitudes appear to have lower hazard rates for obesity (214). Table 1 summarizes the studies conducted in several countries that estimated the prevalence of obesity in representative populations residing at $\geq$ 1500 m (50, 207, 208, 212, 213, 215–221). It appears that obesity prevalence is inversely proportional to altitude. This relationship has been confirmed in a recent study (see Figure 1 in Ref. 208). Notably, this inverse association between obesity prevalence and altitude has been reported to be independent of lifestyle (208, 213, 222), ethnicity (208, 222), ambient temperature (222), air pollution, health insurance coverage, income, emigration rate, and latitude (208).

2. Obesity in children

Lower prevalence of obesity at higher altitudes has also been reported among children in Argentina (223, 224), with no differences in prevalence between girls and boys (223). Surprisingly, children residing at very high altitude did not show differences in fasting glycemia compared with those residing at low altitude (224). This latter finding suggests that the differences in fasting glycemia between lowlanders and highlanders may vary with age, possibly with a late onset, further supporting the concept of an acquired trait. Intriguingly, a study of a small cohort (nonrepresentative) of Arabian children found a higher prevalence of obesity at high altitude (225), raising the possibility that among children, the inverse association between prevalence of obesity and altitude could depend on ethnicity.

B. Possible factors contributing to the lower prevalence of obesity

The effects of altitude exposure on energy metabolism, weight loss, and obesity have been reviewed elsewhere (198, 226, 227). However, most of the evidence discussed in previous reviews originates from studies examining the effect of short-term exposure to altitude on lowlanders. Here we will mainly focus on studies conducted in highlanders.

1. Energy expenditure and food intake

Although human studies exploring the effect of subacute exposure to high and very high altitude on energy expenditure have shown higher basal metabolic rate (228–231), associated with lower BMI (232), studies

Table 1. Prevalence of Obesity in Adult Populations Living at or Above 1500 m

First Author, Year (Ref)	Population	Altitude, m	n	Age, y	Diagnosis Criteria	BMI, kg/m^2	Crude Prevalence, %	Age-Adjusted Prevalence, %
Chen, 2011 (221)	Lhasa, Tibet, China	3658–4200	1289	≥18	N.A.	>28	16.7	
Malaga, 2010 (216)	Lari, Peru	3600	74	>18	N.A.	≥30	8.7	
Medina, 2006 (215)	Arequipa, Peru	2390[a]	1878	20–80	WHO, 2000	≥30		17.6
Mohanna, 2006 (217)	San Pedro de Cajas, Peru	4100	102	≥30	ATP III, 2002	≥30	10.8	
Negi, 2012 (220)	Spiti Valley, India	3900	242	≥20	Consensus, India	≥25	17.4	
	Spiti Valley, India	3100	171	≥20	Consensus, India	≥25	35.7	
Pajuelo-Ramirez, 2010 (50)	Peru	≥3000	959	≥20	WHO, 1997	≥30	8.5	
	Peru	1000–2999	808	≥20	WHO, 1997	≥30	11	
	Peru	<1000	2425	≥20	WHO, 1997	≥30	17.5	
Schargrodsky, 2008 (219)	Quito, Ecuador	2800	1638	25–64	ATP III, 2002	≥30		16.3
	Bogota, Colombia	2625	1553	25–64	ATP III, 2002	≥30		18
	Mexico City, Mexico	2240	1722	25–64	ATP III, 2002	≥30		31
	Barquisimeto, Venezuela	564	1848	25–64	ATP III, 2002	≥30		25.1
	Santiago, Chile	520	1655	25–64	ATP III, 2002	≥30		26.6
	Lima, Peru	153	1652	25–64	ATP III, 2002	≥30		22.3
	Buenos Aires, Argentina	10	1482	25–64	ATP III, 2002	≥30		19.7
Seclén, 1999 (207)	Huaraz, Peru	3052	77	>18	NIH-US, 1985	≥27	18.3	
	Waiku, Amazon, Peru	600	54	>18	NIH-US, 1985	≥27	0	
	Tarapoto, Amazon, Peru	333	90	>18	NIH-US, 1985	≥27	17	
	Cuñumbuque, Amazon, Peru	300	101	>18	NIH-US, 1985	≥27	10.9	
	Lima, Peru	123	158	>18	NIH-US, 1985	≥27	22.8	
	Castilla, Peru	30	118	>18	NIH-US, 1985	≥27	36.7	
Segura, 2006 (212)	Andes, Peru	3493[a]	N.A.	>18	N.A.	≥30	9.1	
	Andes, Peru	2351[a]	N.A.	>18	N.A.	≥30	8.7	
	Amazon, Peru	168.5[a]	1630	>18	N.A.	≥30	11.7	
	Coast, Peru	31.5[a]	7725	>18	N.A.	≥30	13.5	
Shah, 2004 (218)	Ghizer, Pakistan	1675–1980[b]	4203	≥18	WHO, 2000	≥30	2.3	
Sherpa, 2010 (213)	Lhasa, Tibet, China	3660	371	30–70	WHO, 2000	≥30	9.7	
	Nepal	2900	119	30–70	WHO, 2000	≥30	11.8	
	Nepal	1200	127	30–70	WHO, 2000	≥30	19.7	
Woolcott, 2014 (208)	United States	<1500	N.A.	≥20	ATP II, 1998	≥30		30.6
	United States	≥1500	N.A.	≥20	ATP II, 1998	≥30		23.3

Abbreviations: ATP, Adult Treatment Panel; NIH-US, National Institutes of Health-United States; WHO, World Health Organization; N.A., information not available. Studies were selected on the basis that they were conducted in at least one representative population residing at or above 1500 m.

[a] Median altitude of the cities sampled, using altitude values obtained online.

[b] Altitude range is provided elsewhere (268).

comparing basal metabolic rate between lowlanders and highlanders have reported no differences (233, 234). It would be informative to determine whether differences exist in total energy expenditure or nonbasal metabolic rate. For example, one possibility is that unintentional physical activity, which is also an important component of total energy expenditure (235), could be increased among highlanders because living at high altitude may require a higher energy demand to walk in steep topographical terrains. Because ambient temperature is inversely related to geographical elevation (21), cold temperatures at high altitudes could favor increased thermogenesis. This is possible because many communities located at very high altitudes around the world lack the facilities to adjust the temperature of their local environments (eg, home, work).

In a synergistic manner, thyroid hormones and catecholamines induce thermogenesis (236). Although the active forms of T_3 (free T_3) and T_4 (free T_4) and basal norepinephrine have been reported to be higher in highlanders (237–239), the interpretation of these findings is difficult because it is not clear whether subjects were matched for BMI or physical activity. A recent study examining the effect of chronic exposure to 4500–4800 m in humans who reside near sea level showed persistent sympathetic hyperactivation, as determined by heart rate variability, for up to 18 months of stay at very high altitude (240). However, subjects had no changes in BMI. The findings from these studies do not conclusively support or refute higher energy expenditure in highlanders. What is unquestionable is the higher energy expenditure after short-term exposure to high altitudes (198).

Acute exposure to altitude induces loss of appetite (241, 242), which may be related to increased leptin, an

anorexigenic hormone, and decreased ghrelin and cholecystokinin plasma levels (169–171). However, the association between leptin and altitude appears to be different in individuals living at high altitudes because lower leptin levels have been reported in this population (45, 243, 244), even when leptin values are normalized to body fat mass (45). Because leptin is involved in thermoregulation, the lower leptin values in residents of higher altitudes may

Table 2. Prevalence of Diabetes in Adult Populations Living at or Above 1500 m

First Author, Year (Ref)	Population	Altitude, m	n	Age, y	Diagnosis Criteria	Glycemia, mg/dL	Crude Prevalence, %	Age-Adjusted Prevalence, %
Al-Habori, 2004 (249)	Sana, Yemen	2300	498	25–65	WHO, 1999	≥126 or 2-h OGTT ≥200	4.6	
Chen, 2011 (221)	Lhasa, Tibet, China	3658–4200	1289	≥18	N.A.	≥126 or 2-h OGTT ≥200 or self-report	2.9	
Faeh, 2009 (250)	German-speaking Switzerland	259–300	N.A.	40–84		Self-report	5.8	
	German-speaking Switzerland	300–600	N.A.	40–84		Self-report	3.8	
	German-speaking Switzerland	600–900	N.A.	40–84		Self-report	3.4	
	German-speaking Switzerland	900–1200	N.A.	40–84		Self-report	4.0	
	German-speaking Switzerland	1200–1500	N.A.	40–84		Self-report	4.3	
	German-speaking Switzerland	1500–1960	N.A.	40–84		Self-report	5.1	
Malaga, 2010 (216)	Lari, Peru	3600	74	>18	N.A.	≥126	1.3	
Negi, 2012 (220)	Spiti Valley, India	3900	242	≥20	N.A.	≥126	0.4	
	Spiti Valley, India	3100	171	≥20	N.A.	≥126	4.1	
Pajuelo-Ramirez, 2010 (50)	Peru	≥3000	959	≥20	ADA, 1997	≥126	0.9	
	Peru	1000–2999	808	≥20	ADA, 1997	≥126	1.6	
	Peru	<1000	2425	≥20	ADA, 1997	≥126	2.9	
Posadas-Romero, 1994 (248)	Mexico City, Mexico	2255[a]	805	20–90	WHO, 1985	≥140 or self-report	8.7	
Schargrodsky, 2008 (219)	Quito, Ecuador	2800	1638	25–64	ADA, 2003	≥126 or self-report		5.9
	Bogota, Colombia	2625	1553	25–64	ADA, 2003	≥126 or self-report		8.1
	Mexico City, Mexico	2240	1722	25–64	ADA, 2003	≥126 or self-report		8.9
	Barquisimeto, Venezuela	564	1848	25–64	ADA, 2003	≥126 or self-report		6.0
	Santiago, Chile	520	1655	25–64	ADA, 2003	≥126 or self-report		7.2
	Lima, Peru	153	1652	25–64	ADA, 2003	≥126 or self-report		4.4
	Buenos Aires, Argentina	10	1482	25–64	ADA, 2003	≥126 or self-report		6.2
Seclén, 1999 (207)	Huaraz, Peru	3052	77	>18	WHO, 1985	≥140 or 2-h OGTT ≥200	1.3	
	Waiku, Amazon, Peru	600	54	>18	WHO, 1985	≥140 or 2-h OGTT ≥200	3.7	
	Tarapoto, Amazon, Peru	333	90	>18	WHO, 1985	≥140 or 2-h OGTT ≥200	4.4	
	Cuñumbuque, Amazon, Peru	300	101	>18	WHO, 1985	≥140 or 2-h OGTT ≥200	2.0	
	Lima, Peru	123	158	>18	WHO, 1985	≥140 or 2-h OGTT ≥200	7.6	
	Castilla, Peru	30	118	>18	WHO, 1985	≥140 or 2-h OGTT ≥200	6.7	
Segura, 2006 (212)	Andes, Peru	3493[a]	N.A.	>18	-	Self-report	1.8	
	Andes, Peru	2351[a]	N.A.	>18	-	Self-report	2.4	
	Amazon, Peru	168.5[a]	1630	>18	-	Self-report	3.9	
	Coast, Peru	31.5[a]	7725	>18	-	Self-report	4.3	
Woolcott, 2014 (208)	United States	<1500	N.A.	≥20	-	Self-report		9.1
	United States	≥1500	N.A.	≥20	-	Self-report		6.4

Abbreviations: ADA, American Diabetes Association; OGTT, oral glucose tolerance test; WHO, World Health Organization; N.A., information not available. Studies were selected on the basis that they were conducted in at least one representative population residing at or above 1500 m.

[a] Median altitude of the cities sampled, using altitude values obtained online.

represent an adaptive mechanism in response to colder ambient temperatures. However, less clear is whether an association between lower leptin levels and appetite exists in the long term.

2. Poverty and nutrition

It can be argued that populations living at higher altitudes may have lower incomes. Thus, the lower prevalence of obesity at higher altitudes could be associated with poverty. In fact, the lowest BMI values have been reported among populations with the poorest wealth quintiles (245). However, in the United States, for example, the contribution of poverty to the lower prevalence of obesity at higher altitudes is not clear because low income is less frequent at higher altitudes (208). Moreover, the inverse association between obesity and altitude has been reported to be independent of income (208, 222).

As discussed earlier, there is no evidence suggesting intestinal malabsorption below 5000 m (166–168). Therefore, it is unlikely that chronic malabsorption explains differences in BMI between lowlanders and highlanders. However, regional diet may vary considerably among places located at different altitudes. For example, in the Peruvian Andes, cereals constitute a major food ingredient up to 3500 m, whereas at higher altitudes tubers, mainly potatoes, constitute the main component of the diet (246). Although the inverse association between altitude and obesity remains while adjusting for self-reported fruit and vegetable consumption (208, 222), it is possible that differences in the consumption of other food products may account for the lower prevalence of obesity in populations living at higher altitudes.

C. Association between diabetes and altitude

The lower prevalence of diabetes at higher altitudes has been reported in certain groups, including hospital inpatients (205) and soldiers (206), and also in the general population, including large cohorts (207) and nationally representative populations from Peru and the United States (50, 208). Conversely, a small report found no association between diabetes and altitude among Swiss individuals (247). However, 98% of the studied population lived below 1200 m, undermining the power to detect any association.

Table 2 summarizes the studies conducted around the world estimating the prevalence of diabetes in representative populations located at ≥ 1500 m (50, 207, 208, 212, 216, 219–221, 247–250). A trend for an inverse association appears to exist between the prevalence of diabetes and altitude. Indeed, this has been confirmed using county-level data from a nationally representative population of the United States (208). Remarkably, the odds of having obesity and diabetes are approximately 25% and 12% lower, respectively, in individuals living between 1500 and 3500 m than those living below 500 m, while adjusting for multiple factors including self-reported food consumption, physical activity, ethnicity, air pollution, health insurance coverage, income, emigration rate, and latitude

Figure 6.

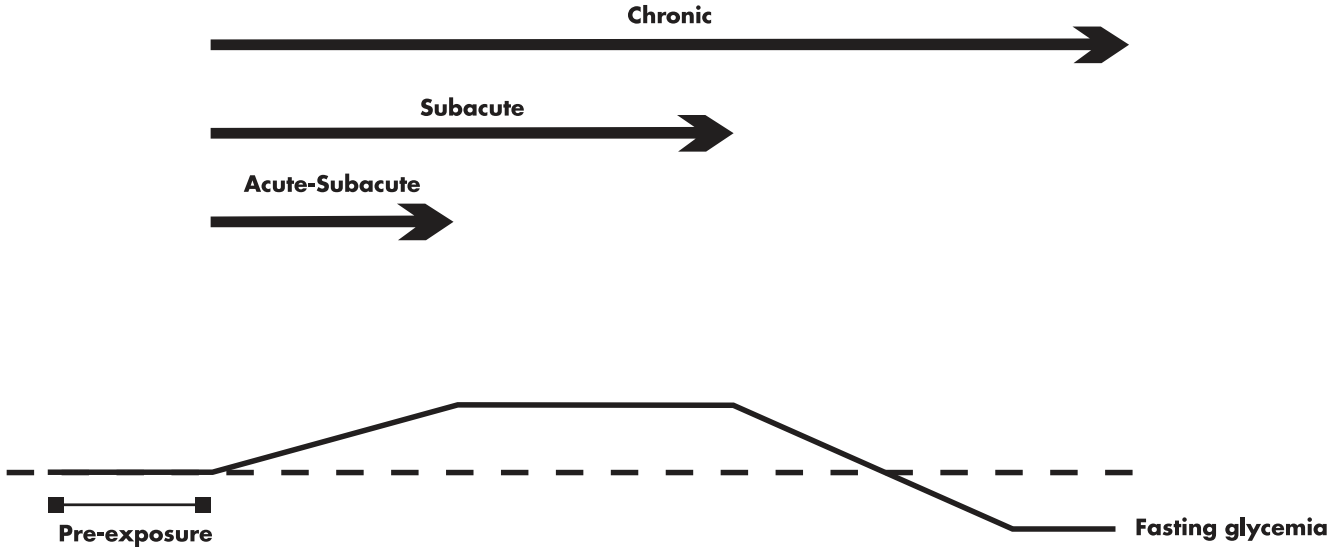

Figure 6. Hypothetical variability of fasting glycemia in nondiabetic humans exposed to natural high or very high altitude. It is possible that the variability of glycemia could also be related to the magnitude of the elevation, with more pronounced changes in glycemia (lowering effect) and faster shifts at higher altitudes. However, this is still speculative. Definitions of acute, subacute, and chronic terms are arbitrary. See Introduction for explanation.

(208). Because the latter study utilized data from a telephone-based survey and diabetes was self-reported, whether the inverse association between diabetes and altitude represents cases of type 1 or type 2 diabetes still remains unknown.

D. Possible factors contributing to the lower prevalence of diabetes

Because obesity is a known risk factor for type 2 diabetes (209, 210), the lower prevalence of obesity at higher altitudes should explain the lower prevalence of diabetes at higher altitudes. However, the lower odds of prevalent diabetes at high altitude remained while adjusting for BMI (208), suggesting that the inverse association between diabetes and altitude may not be accounted for obesity, although it is possible that this association may be mediated by body fat. There is also evidence that ethnicity and access to health care may not account for this association (208, 251).

Figure 7.

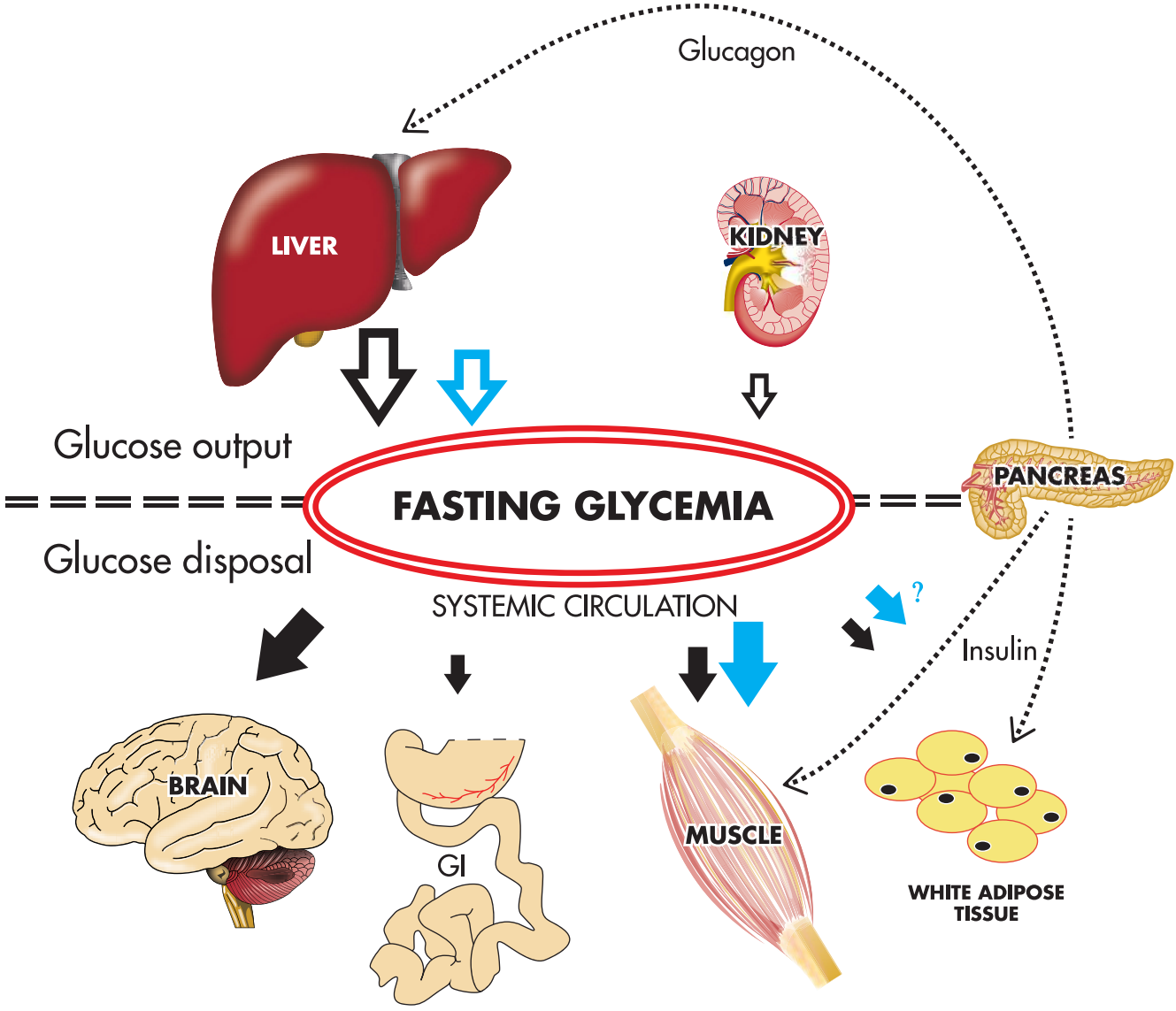

Figure 7. Hypothetical schematic to explain the lower fasting glycemia in healthy individuals living at higher altitudes. The lower fasting glycemia occurs despite similar or lower fasting insulin values as compared to lowlanders (40, 41, 45, 47, 48). In the fasting state, the liver is responsible for maintaining relatively constant the fasting glycemia, contributing up to 80% of the total endogenous glucose production (83). Moreover, there is evidence of a more rapid glucose disposal in highlanders after iv glucose administration (42, 46, 122). Based on these findings, and the evidence of increased skeletal glucose uptake in response to anoxia/hypoxia (116, 144–151, 153), we propose that in the highlander, a lower hepatic glucose output (open blue arrow) and a higher glucose disposal in the skeletal muscle (and probably in the adipose tissue) (solid blue arrows) may account for the lower fasting glycemia as compared with the lowlander (black arrows). For clarity purposes, the substantial fraction of glucose disposal in the liver and kidneys (259, 267) is not represented in the scheme. GI, gastrointestinal tract.

Figure 8.

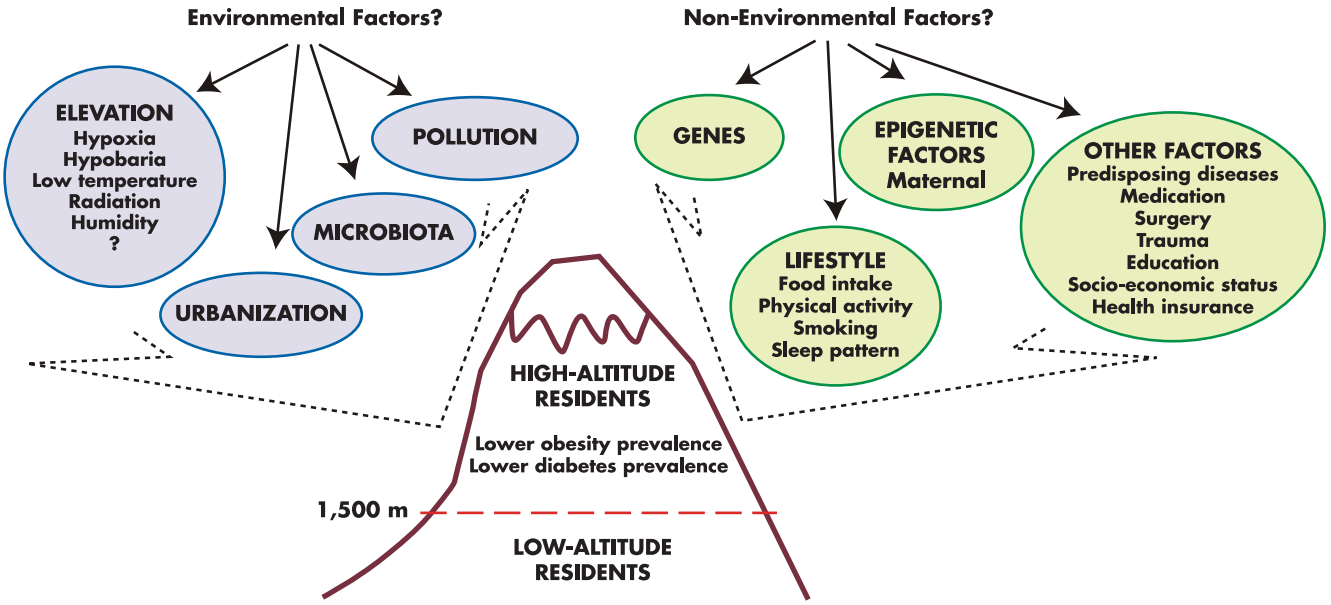

Figure 8. Factors linked to obesity and diabetes. Although nonenvironmental factors have been shown to have a stronger association with obesity and diabetes, several studies have confirmed a link between environmental factors and these clinical conditions. Among these factors, geographical elevation has been associated with lower prevalence of obesity and diabetes, independent of several other potential factors (208, 213, 222).

There are some epidemiological studies that have found a link between environmental factors and diabetes. There is evidence of a possible link between vitamin D (and solar radiation) and diabetes (252). Because solar ultraviolet (UV)-B radiation increases proportionally to altitude (approximately by 7% every kilometer) (253), the possibility that the lower prevalence of diabetes at higher altitudes could be accounted for by solar radiation should be considered. However, this latter possibility seems to be unlikely because administration of vitamin D_2 in humans has failed to modify insulin sensitivity (254), a key component in the pathogenesis of diabetes. Moreover, a recent meta-analysis has concluded that administration of vitamin D_3 had no effect on incident diabetes (255).

Air pollution, predominantly fine particulate matter, has also been linked to the pathogenesis of type 2 diabetes (256, 257). Although the concentration of fine particulate matter is lower at higher altitudes (258), the association between diabetes and altitude remains after adjustment for air pollution, including particle matter ≤ 2.5 μm and ozone levels (208).

It should be clear that the inverse association between altitude and diabetes does not prove causality. However, the robust evidence in vivo of a lower glycemia (40–43, 45–48) and greater glucose disposal (38, 42, 46, 48, 122, 123) among individuals living at higher altitudes, together with the evidence in vitro of a direct stimulatory effect of anoxia on glucose uptake in the skeletal muscle (144–151), provides some biological explanation for the lower prevalence of diabetes at higher elevations.

X. Summary and Conclusions

Sudden exposure to high or very high altitude may initially lead to fasting hyperglycemia. However, the acclimatization process, as the exposure continues, may attenuate this response. Conversely, chronic or permanent exposure to high altitudes may lower fasting glycemia and glycemia postglucose challenge (40–48, 123), and it is likely to be acquired. The hypothetical variability in fasting glycemia as a function of exposure time to high altitudes is simplified in Figure 6.

The physiological changes in the human body that determine the lower fasting glycemia among highlanders are not fully understood. However, insulin is unlikely to be involved. Studies showing higher glucagon levels in highlanders and reduced hepatic glycogen content in rodents chronically exposed to hypoxia suggest that the liver may play a role. Less clear is the possible contribution of the gut because most of the studies have focused on the short-term exposure to high altitudes. To date, no study has assessed HGO or peripheral insulin sensitivity in vivo in individuals permanently living at high altitudes. However, there is

strong evidence in vivo of a greater glucose disposal during iv glucose administration in permanent residents of high altitudes (42, 46, 122). Moreover, the findings from in vitro studies clearly show that virtual anoxia increases glucose uptake in cultured skeletal muscle from rodents and humans (144–151), most likely linked to increased GLUT4 translocation and GLUT4 content, via the AMPK-dependent pathway and HIF activation. However, the direct effect of hypoxia on glucose uptake in cultured skeletal muscle has not yet been demonstrated.

In the postabsorptive state, blood glucose supply depends primarily on the liver (83), whereas glucose disposal occurs primarily in the brain (~50%) and to a lesser extent in the skeletal muscle (<25%) (259). This widely accepted concept, together with the evidence of higher glucose disposal in vivo in highlanders and increased glucose uptake in the skeletal muscle induced by anoxia and hypoxia in vivo, lead us to hypothesize that the lower fasting glycemia in individuals living at high altitudes is determined by a lower HGO and a higher glucose disposal in the skeletal muscle. This concept is summarized in Figure 7.

The inverse association between obesity and altitude is well documented, and it remains while adjusting for multiple risk factors (208, 213, 222). Likewise, an inverse association between diabetes and altitude, while adjusting for several factors (including BMI), has also been recently demonstrated (208), but longitudinal clinical studies will be required to determine causality. Figure 8 depicts the complexity of possible factors related to the lower prevalence of obesity and diabetes, including geographical elevation. A recent quasi-experimental study in a military population provides further evidence that altitude could have a direct effect on the pathogenesis of obesity (214).

Further experimental studies aiming to determine the altitude threshold and minimum exposure duration needed to influence blood glucose levels may have an important clinical impact. The use of simulated altitude or hypoxia alone would be more practical, but future studies are required to determine whether these approaches lead to similar or better results than those obtained under natural altitude conditions. So far, small clinical studies have shown that hypoxic sessions may improve glucose homeostasis in overweight, obese, and type 2 diabetic subjects (115–117, 260). However, no effects of simulated altitude (whether hypobaric or normobaric hypoxia) have yet been monitored for periods longer than 10 weeks (260). The question also remains as to whether simulated altitude could be widely used as a potential clinical intervention for metabolic disorders. Perhaps hypoxia could be useful as a concomitant therapy rather than as a substitution of conventional approaches.

Concern about the clinical applicability of hypoxia has been raised, given that obstructive sleep apnea (OSA), which is associated with oxygen desaturation, has been linked to impaired insulin sensitivity and higher risk of diabetes (261, 262). However, OSA is a disorder manifested not only by repeated and transitory events of extremely variable oxygen desaturation (oxygen saturation can range from 90 to 50%), but also by blood CO_2 retention (263). In addition, OSA is highly associated with obesity (262). Whether the association between sleep apnea and metabolic alterations is independent of CO_2 retention or obesity still remains elusive. What appears to be clear is that severe hypoxia (~5% O_2 inspired) per se decreases insulin sensitivity (112, 113), whereas moderate hypoxia (13–15% O_2) rather improves insulin sensitivity (115, 116).

Finally, although genetic population studies support the hypothesis that the HIF pathway may play a role in the mechanisms of adaptation to high altitude, whether hypoxia is the only determinant of the genetic adaptation to high altitudes remains to be explored. Understanding the mechanisms that regulate and maintain the lower fasting glycemia in individuals who live at higher altitudes could lead to new therapeutics for impaired glucose homeostasis.

Acknowledgments

This paper is dedicated to the memory of Dr Javier Torres Noriega (1950–2013), who devoted decades to mentoring many pre- and postgraduate students in the field of endocrine and high-altitude physiology at the Universidad Nacional Mayor de San Marcos, Peru.

We thank Mrs Nelly Diaz and Mr Frank Martínez for their valuable help in obtaining historical publications. We also thank Dr Oscar Castillo (Instituto Nacional de Biología Andina, Universidad Nacional Mayor de San Marcos, Peru) for thoughtful discussion on many sections of the present review.

Address requests for reprints to: Orison O. Woolcott, MD, Diabetes and Obesity Research Institute, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Thalians E104, Los Angeles, CA 90048. E-mail: Orison.Woolcott@cshs.org.

This study was supported by National Institutes of Health Grants DK29867 and DK27619 (to R.N.B.).

Disclosure Summary: The authors disclose no conflict of interest relevant to this work.

References

1. **West JB.** The physiologic basis of high-altitude diseases. *Ann Intern Med*. 2004;141:789–800.
2. **Beall CM.** Adaptations to altitude: a current assessment. *Annu Rev Anthropol*. 2001;30:423–456.

3. **Weil JV, Zwillich CW.** Assessment of ventilatory response to hypoxia: methods and interpretation. *Chest*. 1976;70:124–128.
4. **Peacock AJ.** ABC of oxygen: oxygen at high altitude. *BMJ*. 1998;317:1063–1066.
5. **Blume FD.** Metabolic and endocrine changes at altitude. In: West JB, Lahiri S, eds. *High Altitude and Man*. Bethesda, MD: American Physiological Society; 1984:37–45.
6. **Kellogg RH.** Some high points in high altitude. In: Folinsbee LJ, Wagner JA, Borgia JF, Drinkwater BL, Gliner JA, Bedi JF, eds. *Environmental Stress. Individual Human Adaptations*. New York, NY: Academic Press, Inc; 1978:317–323.
7. **Bert P.** *Barometric Pressure: Researches in Experimental Physiology* [first published in French in 1878]. Columbus, OH: College Book Company; 1943.
8. **Columbia University Center for International Earth Science Information Network.** National Aggregates of Geospatial Data Collection: Population, Landscape, and Climate Estimates (PLACE II), version 2 (1990, 2000). http://sedac.ciesin.columbia.edu/data/set/nagdc-population-landscape-climate-estimates-v2. Accessed April 28, 2014.
9. **Cohen JE, Small C.** Hypsographic demography: the distribution of human population by altitude. *Proc Natl Acad Sci USA*. 1998;95:14009–14014.
10. **Burrows SM, Elbert W, Lawrence MG, Poschl U.** Bacteria in the global atmosphere – Part 1: review and synthesis of literature data for different ecosystems. *Atmos Chem Phys*. 2009;9:9263–9280.
11. **Heath D, Williams DR.** The environment. In: Heath D, Williams DR, eds. *Man at High Altitude: The Pathophysiology of Acclimatization and Adaptation*. Edinburgh, UK: Churchill Livingstone; 1977:4–14.
12. **Millet GP, Faiss R, Pialoux V.** Last word on Point: Counterpoint: hypobaric hypoxia induces different responses from normobaric hypoxia. *J Appl Physiol*. 2012;112:1795.
13. **Mounier R, Brugniaux JV.** Last word on Counterpoint: hypobaric hypoxia does not induce different physiological responses from normobaric hypoxia. *J Appl Physiol*. 2012;112:1796.
14. **Luks AM, Swenson ER.** Pulse oximetry at high altitude. *High Alt Med Biol*. 2011;12:109–119.
15. **Arias-Stella J, Recavarren S.** Right ventricular hypertrophy in native children living at high altitude. *Am J Pathol*. 1962;41:55–64.
16. **Reynafarje C, Lozano R, Valdivieso J.** The polycythemia of high altitudes: iron metabolism and related aspects. *Blood*. 1959;14:433–455.
17. **Rupert JL, Hochachka PW.** Genetic approaches to understanding human adaptation to altitude in the Andes. *J Exp Biol*. 2001;204:3151–3160.
18. **Heath D, Williams DR.** The physique of high altitude man. In: Heath D, Williams DR, eds. *Man at High Altitude: The Pathophysiology of Acclimatization and Adaptation*. Edinburgh, UK: Churchill Livingstone; 1977:15–26.
19. **Mirrakhimov MM.** Biological and physiological characteristics of the high-altitude natives of Tien Shan and the Pamirs. In: Baker PT, ed. *The Biology of High-Altitude Peoples*. Cambridge, UK: Cambridge University Press; 1978:299–315.
20. **Frisancho AR.** Developmental functional adaptation to high altitude: review. *Am J Hum Biol*. 2013;25:151–168.
21. **Larsen JJ, Hansen JM, Olsen NV, Galbo H, Dela F.** The effect of altitude hypoxia on glucose homeostasis in men. *J Physiol*. 1997;504:241–249.
22. **Sawhney RC, Malhotra AS, Singh T.** Glucoregulatory hormones in man at high altitude. *Eur J Appl Physiol Occup Physiol*. 1991;62:286–291.
23. **Sutton J, Garmendia F.** Hormonal variation during physical exertion at high altitude [in Spanish]. *Arch Biol Andina*. 1977;7:83–93.
24. **Stock MJ, Chapman C, Stirling JL, Campbell IT.** Effects of exercise, altitude, and food on blood hormone and metabolite levels. *J Appl Physiol*. 1978;45:350–354.
25. **Consolazio CF, Johnson HL, Krzywicki HJ, Daws TA.** Metabolic aspects of acute altitude exposure (4,300 meters) in adequately nourished humans. *Am J Clin Nutr*. 1972;25:23–29.
26. **Sawhney RC, Malhotra AS, Singh T, Rai RM, Sinha KC.** Insulin secretion at high altitude in man. *Int J Biometeorol*. 1986;30:231–238.
27. **Johnson HL, Consolazio CF, Burk RF, Daws TA.** Glucose-14 C-UL metabolism in man after abrupt altitude exposure (4,300 m). *Aerosp Med*. 1974;45:849–854.
28. **Brooks GA, Butterfield GE, Wolfe RR, et al.** Increased dependence on blood glucose after acclimatization to 4,300 m. *J Appl Physiol*. 1991;70:919–927.
29. **Rostrup M.** Catecholamines, hypoxia and high altitude. *Acta Physiol Scand*. 1998;162:389–399.
30. **Richalet JP.** The endocrine system. In: Hornbein TF, Schoene RB, eds. *High Altitude. An Exploration of Human Adaptation*. New York: Marcel Dekker, Inc; 2001;601–644.
31. **Woods DR, Stacey M, Hill N, de Alwis N.** Endocrine aspects of high altitude acclimatization and acute mountain sickness. *J R Army Med Corps*. 2011;157:33–37.
32. **Braun B, Mawson JT, Muza SR, et al.** Women at altitude: carbohydrate utilization during exercise at 4,300 m. *J Appl Physiol (1985)*. 2000;88:246–256.
33. **Brahmachari HD, Malhotra MS, Joseph S, Krishnan UR.** Glucose tolerance at high altitude in man. *Indian J Med Res*. 1973;61:411–415.
34. **Young PM, Sutton JR, Green HJ, et al.** Operation Everest II: metabolic and hormonal responses to incremental exercise to exhaustion. *J Appl Physiol*. 1992;73:2574–2579.
35. **Boutwell JH, Cilley JH, Krasno LR, Ivy AC, Farmer CJ.** Effect of repeated exposure of human subjects to hypoxia on glucose tolerance, excretion of ascorbic acid, and phenylalanine tolerance. *J Appl Physiol*. 1950;2:388–392.
36. **Brooks GA, Wolfel EE, Groves BM, et al.** Muscle accounts for glucose disposal but not blood lactate appearance during exercise after acclimatization to 4,300 m. *J Appl Physiol (1985)*. 1992;72:2435–2445.
37. **Hochachka PW, Stanley C, Matheson GO, McKenzie DC, Allen PS, Parkhouse WS.** Metabolic and work efficiencies during exercise in Andean natives. *J Appl Physiol (1985)*. 1991;70:1720–1730.
38. **Holden JE, Stone CK, Clark CM, et al.** Enhanced cardiac metabolism of plasma glucose in high-altitude natives: ad-

aptation against chronic hypoxia. *J Appl Physiol*. 1995; 79:222–228.
39. **Braun B.** Effects of high altitude on substrate use and metabolic economy: cause and effect? *Med Sci Sports Exerc*. 2008;40:1495–1500.
40. **Castillo O, Woolcott OO, Gonzales E, et al.** Residents at high altitude show a lower glucose profile than sea-level residents throughout 12-hour blood continuous monitoring. *High Alt Med Biol*. 2007;8:307–311.
41. **Garmendia F, Torres J, Tamayo R, Urdanivia E.** Contributions to the knowledge of glycemia at high altitude [in Spanish]. *Arch Inst Biol Andina*. 1972;5:51–56.
42. **Calderón R, Llerena A.** Carbohydrate metabolism in people living in chronic hypoxia. *Diabetes*. 1965;14:100–105.
43. **Picon-Reategui E, Buskirk ER, Baker PT.** Blood glucose in high-altitude natives and during acclimatization to altitude. *J Appl Physiol*. 1970;29:560–563.
44. **Srivastava KK, Kumria MM, Grover SK, Sridharan K, Malhotra MS.** Glucose tolerance of lowlanders during prolonged stay at high altitude and among high altitude natives. *Aviat Space Environ Med*. 1975;46:144–146.
45. **Lindgärde F, Ercilla MB, Correa LR, Ahrén B.** Body adiposity, insulin, and leptin in subgroups of Peruvian Amerindians. *High Alt Med. Biol*. 2004;5:27–31.
46. **Calderón R, Llerena LA, Munive L, Kruger F.** Intravenous glucose tolerance test in pregnancy in women living in chronic hypoxia. *Diabetes*. 1966;15:130–132.
47. **Krampl E, Kametas NA, Nowotny P, Roden M, Nicolaides KH.** Glucose metabolism in pregnancy at high altitude. *Diabetes Care*. 2001;24:817–822.
48. **Zamudio S, Torricos T, Fik E, et al.** Hypoglycemia and the origin of hypoxia-induced reduction in human fetal growth. *PLoS One*. 2010;5:e8551.
49. **Jo N, Garmendia F, Damas G, Pando R, Saavedra S.** Lower insulin resistance in obese people from high altitude [in Spanish]. *An Fac Med Lima*. 1997;58:109–111.
50. **Pajuelo-Ramírez J, Sánchez-Abanto J, Arbañil-Huamán H.** Non-transmissible chronic diseases in Peru and their relationship with altitude [in Spanish]. *Rev Soc Peru Med Interna*. 2010;23:45–52.
51. **Picón-Reátegui E.** Effect of chronic hypoxia on the action of epinephrine in carbohydrate metabolism. *J Appl Physiol*. 1966;21:1181–1184.
52. **Garmendia F, Arroyo J, Muro M.** Blood sugar of the normal high altitude native [in Spanish]. *Arch Inst Biol Andina*. 1970;3:209–216.
53. **Foll M, Gaggiotti OE, Daub JT, Vatsiou A, Excoffier L.** Widespread signals of convergent adaptation to high altitude in Asia and America. *Am J Hum Genet*. 2014;95: 394–407.
54. **Bigham AW, Wilson MJ, Julian CG, et al.** Andean and Tibetan patterns of adaptation to high altitude. *Am J Hum Biol*. 2013;25:190–197.
55. **Xing G, Qualls C, Huicho L, et al.** Adaptation and maladaptation to ambient hypoxia; Andean, Ethiopian and Himalayan patterns. *PLoS One*. 2008;3:e2342.
56. **Oberg D, Ostenson CG.** Performance of glucose dehydrogenase-and glucose oxidase-based blood glucose meters at high altitude and low temperature. *Diabetes Care*. 2005; 28:1261.
57. **de Mol P, Krabbe HG, de Vries ST, et al.** Accuracy of handheld blood glucose meters at high altitude. *PLoS One*. 2010;5:e15485.
58. **Gautier JF, Bigard AX, Douce P, Duvallet A, Cathelineau G.** Influence of simulated altitude on the performance of five blood glucose meters. *Diabetes Care*. 1996;19:1430–1433.
59. **Olateju T, Begley J, Flanagan D, Kerr D.** Effects of simulated altitude on blood glucose meter performance: implications for in-flight blood glucose monitoring. *J Diabetes Sci Technol*. 2012;6:867–874.
60. **Baumstark A, Schmid C, Pleus S, Haug C, Freckmann G.** Influence of partial pressure of oxygen in blood samples on measurement performance in glucose-oxidase-based systems for self-monitoring of blood glucose. *J Diabetes Sci Technol*. 2013;7:1513–1521.
61. **Pecchio O, Maule S, Migliardi M, Trento M, Veglio M.** Effects of exposure at an altitude of 3,000 m on performance of glucose meters. *Diabetes Care*. 2000;23:129–131.
62. **King JM, Eigenmann CA, Colagiuri S.** Effect of ambient temperature and humidity on performance of blood glucose meters. *Diabet Med*. 1995;12:337–340.
63. **Chmielewski SA, Kurtock DK, Jennings SA, et al.** Precision and accuracy of the Accu-Chek Advantage blood glucose monitoring system at high altitude. *Clin Chem*. 1996;42: 115–117.
64. **Giordano BP, Thrash W, Hollenbaugh L, et al.** Performance of seven blood glucose testing systems at high altitude. *Diabetes Educ*. 1989;15:444–448.
65. **Tang Z, Louie RF, Payes M, Chang KC, Kost GJ.** Oxygen effects on glucose measurements with a reference analyzer and three handheld meters. *Diabetes Technol Ther*. 2000; 2:349–362.
66. **Laurinavicius V, Kurtinaitiene B, Liauksminas V, et al.** Oxygen insensitive glucose biosensor based on PQQ-dependent glucose dehydrogenase. *Anal Lett*. 1999;32:299–316.
67. **Ginsberg BH.** Factors affecting blood glucose monitoring: sources of errors in measurement. *J Diabetes Sci Technol*. 2009;3:903–913.
68. **Rao LV, Jakubiak F, Sidwell JS, Winkelman JW, Snyder ML.** Accuracy evaluation of a new glucometer with automated hematocrit measurement and correction. *Clin Chim Acta*. 2005;356:178–183.
69. **Tang Z, Lee JH, Louie RF, Kost GJ.** Effects of different hematocrit levels on glucose measurements with handheld meters for point-of-care testing. *Arch Pathol Lab Med*. 2000;124:1135–1140.
70. **Billington CJ, Casciato DA, Choquette DL, Morley JE.** Artifactual hypoglycemia associated with polycythemia vera. *JAMA*. 1983;249:774–775.
71. **Field JB, Williams HE.** Artifactual hypoglycemia associated with leukemia. *N Engl J Med*. 1961;265:946–948.
72. **Arnaud J, Gutierrez N.** Human red cell glycolysis in high altitude chronic hypoxia. *Am J Phys Anthropol*. 1984;63: 307–314.
73. **Sacks DB, Arnold M, Bakris GL, et al.** Position statement executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care*. 2011;34:1419–1423.
74. **Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, Mc-**

Donald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem*. 2002;48:436–472.
75. **Krampl E, Kametas NA, Cacho Zegarra AM, Roden M, Nicolaides KH.** Maternal plasma glucose at high altitude. *BJOG*. 2001;108:254–257.
76. **Moret P, Covarrubias E, Coudert J, Duchosal F.** Cardiocirculation adaptation to chronic hypoxia. II. Comparative study of myocardial metabolism of glucose, lactate, pyruvate and free fatty acids between sea level and high altitude residents. *Acta Cardiol*. 1972;27:483–503.
77. **Polonsky KS, Given BD, Hirsch L, et al.** Quantitative study of insulin secretion and clearance in normal and obese subjects. *J Clin Invest*. 1988;81:435–441.
78. **Caumo A, Florea I, Luzi L.** Effect of a variable hepatic insulin clearance on the postprandial insulin profile: insights from a model simulation study. *Acta Diabetol*. 2007; 44:23–29.
79. **Roberts AC, Butterfield GE, Cymerman A, Reeves JT, Wolfel EE, Brooks GA.** Acclimatization to 4,300-m altitude decreases reliance on fat as a substrate. *J Appl Physiol*. 1996;81:1762–1771.
80. **Benso A, Broglio F, Aimaretti G, et al.** Endocrine and metabolic responses to extreme altitude and physical exercise in climbers. *Eur J Endocrinol*. 2007;157:733–740.
81. **Cassinelli M.** Glucose, lactic acid, and piruvic acid at sea level and high altitude [in Spanish]. *An Fac Med*. 1949;32: 1–28.
82. **Dinneen S, Gerich J, Rizza R.** Carbohydrate metabolism in non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1992;327:707–713.
83. **Gerich JE, Meyer C, Woerle HJ, Stumvoll M.** Renal gluconeogenesis: its importance in human glucose homeostasis. *Diabetes Care*. 2001;24:382–391.
84. **Ader M, Bergman RN.** Insulin sensitivity in the intact organism. *Baillieres Clin Endocrinol Metab*. 1987;1:879–910.
85. **Cherrington AD.** Control of glucose production in vivo by insulin and glucagon. In: Pollock DM, ed. *Comprehensive Physiology*. Hoboken, NJ: John Wiley, Sons, Inc; 2010: 759–785.
86. **Roberts AC, Reeves JT, Butterfield GE, et al.** Altitude and β-blockade augment glucose utilization during submaximal exercise. *J Appl Physiol*. 1996;80:605–615.
87. **Andres R, Swerdloff R, Pozefsky T, Coleman D.** Manual feedback technique for the control of blood glucose concentration. In: Skeggs LT, ed. *Automation in Analytical Chemistry*. New York, NY: Mediad, Inc; 1966;486–491.
88. **Lin HV, Accili D.** Hormonal regulation of hepatic glucose production in health and disease. *Cell Metab*. 2011;14:9–19.
89. **Dufour S, Lebon V, Shulman GI, Petersen KF.** Regulation of net hepatic glycogenolysis and gluconeogenesis by epinephrine in humans. *Am J Physiol Endocrinol Metab*. 2009;297:E231–E235.
90. **Vranic M, Miles P, Rastogi K, et al.** Effect of stress on glucoregulation in physiology and diabetes. *Adv Exp Med Biol*. 1991;291:161–183.
91. **Jiang G, Zhang BB.** Glucagon and regulation of glucose metabolism. *Am J Physiol Endocrinol Metab*. 2003;284: E671–E678.
92. **Bergman RN.** Non-esterified fatty acids and the liver: why is insulin secreted into the portal vein? *Diabetologia*. 2000; 43:946–952.
93. **Ader M, Bergman RN.** Peripheral effects of insulin dominate suppression of fasting hepatic glucose production. *Am J Physiol*. 1990;258:E1020–E1032.
94. **Reynafarje-Hurtado C.** Endocrinology. In: Reynafarje-Hurtado C, ed. *The adaptation to high altitudes. Peruvian study contribution* [in Spanish]. Lima, Peru: Concytec; 1990:113–116.
95. **Picon-Reategui E.** Effect of glucagon on carbohydrate metabolism in high-altitude residents. *Arch Biol Andina*. 1981;11:6–15.
96. **Björkman O, Felig P, Wahren J.** The contrasting responses of splanchnic and renal glucose output to gluconeogenic substrates and to hypoglucagonemia in 60-h-fasted humans. *Diabetes*. 1980;29:610–616.
97. **Stumvoll M, Meyer C, Kreider M, Perriello G, Gerich J.** Effects of glucagon on renal and hepatic glutamine gluconeogenesis in normal postabsorptive humans. *Metabolism*. 1998;47:1227–1232.
98. **Ohneda A, Maruhama Y, Itabashi H, Horigome K, Yanbe A.** Diagnostic value of intravenous glucagon test in insulinoma. *Tohoku J Exp Med*. 1975;116:205–211.
99. **Blume FD, Pace N.** Effect of translocation to 3,800 m altitude on glycolysis in mice. *J Appl Physiol*. 1967;23:75–79.
100. **Ou LC.** Hepatic and renal gluconeogenesis in rats acclimatized to high altitude. *J Appl Physiol*. 1974;36:303–307.
101. **Timiras PS, Hill R, Krum AA, Lis AW.** Carbohydrate metabolism in fed and fasted rats exposed to an altitude of 12,470 feet. *Am J Physiol*. 1958;193:415–424.
102. **Wise S, Nielsen M, Rizza R.** Effects of hepatic glycogen content on hepatic insulin action in humans: alteration in the relative contributions of glycogenolysis and gluconeogenesis to endogenous glucose production. *J Clin Endocrinol Metab*. 1997;82:1828–1833.
103. **Vissing J, Wallace JL, Galbo H.** Effect of liver glycogen content on glucose production in running rats. *J Appl Physiol*. 1989;66:318–322.
104. **Andres R, Cader G, Zierler KL.** The quantitatively minor role of carbohydrate in oxidative metabolism by skeletal muscle in intact man in the basal state; measurements of oxygen and glucose uptake and carbon dioxide and lactate production in the forearm. *J Clin Invest*. 1956;35:671–682.
105. **Baron AD, Kolterman OG, Bell J, Mandarino LJ, Olefsky JM.** Rates of noninsulin-mediated glucose uptake are elevated in type II diabetic subjects. *J Clin Invest*. 1985;76: 1782–1788.
106. **Forbes WH.** Blood sugar and glucose tolerance at high altitudes. *Am J Physiol*. 1936;116:309–316.
107. **Chen MT, Lee WC, Chen SC, et al.** Effect of a prolonged altitude expedition on glucose tolerance and abdominal fatness. *Res Q Exerc Sport*. 2010;81:472–477.
108. **Anderwald C, Gastaldelli A, Tura A, et al.** Mechanism and effects of glucose absorption during an oral glucose tolerance test among females and males. *J Clin Endocrinol Metab*. 2011;96:515–524.
109. **Salinari S, Bertuzzi A, Mingrone G.** Intestinal transit of a

glucose bolus and incretin kinetics: a mathematical model with application to the oral glucose tolerance test. *Am J Physiol Endocrinol Metab*. 2011;300:E955–E965.
110. **Mari A, Bagger JI, Ferrannini E, Holst JJ, Knop FK, Vilsbøll T.** Mechanisms of the incretin effect in subjects with normal glucose tolerance and patients with type 2 diabetes. *PLoS One*. 2013;8:e73154.
111. **Ahrén B, Holst JJ, Mari A.** Characterization of GLP-1 effects on β-cell function after meal ingestion in humans. *Diabetes Care*. 2003;26:2860–2864.
112. **Oltmanns KM, Gehring H, Rudolf S, et al.** Hypoxia causes glucose intolerance in humans. *Am J Respir Crit Care Med*. 2004;169:1231–1237.
113. **Louis M, Punjabi NM.** Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. *J Appl Physiol*. 2009;106:1538–1544.
114. **Bergman RN, Ider YZ, Bowden CR, Cobelli C.** Quantitative estimation of insulin sensitivity. *Am J Physiol*. 1979; 236:E667–E677.
115. **Mackenzie R, Maxwell N, Castle P, Brickley G, Watt P.** Acute hypoxia and exercise improve insulin sensitivity (S(I) (2*)) in individuals with type 2 diabetes. *Diabetes Metab Res Rev*. 2011;27:94–101.
116. **Lecoultre V, Peterson CM, Covington JD, et al.** Ten nights of moderate hypoxia improves insulin sensitivity in obese humans. *Diabetes Care*. 2013;36:e197–e198.
117. **Duennwald T, Gatterer H, Groop PH, Burtscher M, Bernardi L.** Effects of a single bout of interval hypoxia on cardiorespiratory control and blood glucose in patients with type 2 diabetes. *Diabetes Care*. 2013;36:2183–2189.
118. **Lee EJ, Alonso LC, Stefanovski D, et al.** Time-dependent changes in glucose and insulin regulation during intermittent hypoxia and continuous hypoxia. *Eur J Appl Physiol*. 2013;113:467–478.
119. **Zinker BA, Namdaran K, Wilson R, Lacy DB, Wasserman DH.** Acute adaptation of carbohydrate metabolism to decreased arterial PO2. *Am J Physiol*. 1994;266:E921–E929.
120. **Derave W, Hespel P.** Role of adenosine in regulating glucose uptake during contractions and hypoxia in rat skeletal muscle. *J Physiol*. 1999;515:255–263.
121. **Wojtaszewski JF, Laustsen JL, Derave W, Richter EA.** Hypoxia and contractions do not utilize the same signaling mechanism in stimulating skeletal muscle glucose transport. *Biochim Biophys Acta*. 1998;1380:396–404.
122. **Picon Reategui E.** Intravenous glucose tolerance test at sea level and at high altitudes. *J Clin Endocrinol Metab*. 1963; 23:1256–1261.
123. **Picon-Reategui E.** Studies on the metabolism of carbohydrates at sea level and at high altitudes. *Metabolism*. 1962; 11:1148–1154.
124. **Saccà L, Cicala M, Trimarco B, Ungaro B, Vigorito C.** Differential effects of insulin on splanchnic and peripheral glucose disposal after an intravenous glucose load in man. *J Clin Invest*. 1982;70:117–126.
125. **Picon-Reategui E.** Insulin, epinephrine, and glucagon on the metabolism of carbohydrates at high altitude. *Fed Proc*. 1966;25:1233–1239.
126. **Grulet H, Durlach V, Hecart AC, Gross A, Leutenegger M.** Study of the rate of early glucose disappearance following insulin injection: insulin sensitivity index. *Diabetes Res Clin Pract*. 1993;20:201–207.
127. **Bonora E, Moghetti P, Zancanaro C, et al.** Estimates of in vivo insulin action in man: comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. *J Clin Endocrinol Metab*. 1989;68:374–378.
128. **Ferrannini E, Mari A.** How to measure insulin sensitivity. *J Hypertens*. 1998;16:895–906.
129. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC.** Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
130. **Wallace TM, Levy JC, Matthews DR.** Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27:1487–1495.
131. **Nuutila P.** Applications of PET in diabetes research. *Horm Metab Res*. 1997;29:337–339.
132. **Howald H, Pette D, Simoneau JA, Uber A, Hoppeler H, Cerretelli P.** Effect of chronic hypoxia on muscle enzyme activities. *Int J Sports Med*. 1990;11(suppl 1):S10–S14.
133. **Cerretelli P, Gelfi C.** Energy metabolism in hypoxia: reinterpreting some features of muscle physiology on molecular grounds. *Eur J Appl Physiol*. 2011;111:421–432.
134. **Murray AJ.** Metabolic adaptation of skeletal muscle to high altitude hypoxia: how new technologies could resolve the controversies. *Genome Med*. 2009;1:117.
135. **Green HJ, Sutton JR.** The effects of altitude on skeletal muscle. In: Hornbein TF, Schoene RB, eds. *High Altitude: An Exploration of Human Adaptation*. New York, NY: Marcel Dekker, Inc; 2001:443–492.
136. **Clanton TL, Hogan MC, Gladden LB.** Regulation of cellular gas exchange, oxygen sensing, and metabolic control. *Compr Physiol*. 2013;3:1135–1190.
137. **Ge RL, Simonson TS, Cooksey RC, et al.** Metabolic insight into mechanisms of high-altitude adaptation in Tibetans. *Mol Genet Metab*. 2012;106:244–247.
138. **Hogan MC, Cox RH, Welch HG.** Lactate accumulation during incremental exercise with varied inspired oxygen fractions. *J Appl Physiol Respir Environ Exerc Physiol*. 1983;55:1134–1140.
139. **Hughson RL, Green HJ, Sharratt MT.** Gas exchange, blood lactate, and plasma catecholamines during incremental exercise in hypoxia and normoxia. *J Appl Physiol (1985)*. 1995;79:1134–1141.
140. **Brooks GA, Butterfield GE, Wolfe RR, et al.** Decreased reliance on lactate during exercise after acclimatization to 4,300 m. *J Appl Physiol (1985)*. 1991;71:333–341.
141. **Randle PJ, Smith GH.** Regulation of glucose uptake by muscle. 1. The effects of insulin, anaerobiosis and cell poisons on the uptake of glucose and release of potassium by isolated rat diaphragm. *Biochem J*. 1958;70:490–500.
142. **Morgan HE, Randle PJ, Regen DM.** Regulation of glucose uptake by muscle. 3. The effects of insulin, anoxia, salicylate and 2:4-dinitrophenol on membrane transport and intracellular phosphorylation of glucose in the isolated rat heart. *Biochem J*. 1959;73:573–579.
143. **Wheeler TJ.** Translocation of glucose transporters in response to anoxia in heart. *J Biol Chem*. 1988;263:19447–19454.
144. **Cartee GD, Douen AG, Ramlal T, Klip A, Holloszy JO.** Stimulation of glucose transport in skeletal muscle by hypoxia. *J Appl Physiol*. 1991;70:1593–1600.
145. **Reynolds TH 4th, Brozinick JT Jr, Rogers MA, Cushman**

SW. Effects of exercise training on glucose transport and cell surface GLUT-4 in isolated rat epitrochlearis muscle. *Am J Physiol*. 1997;272:E320–E325.
146. **Zierath JR, Tsao TS, Stenbit AE, Ryder JW, Galuska D, Charron MJ.** Restoration of hypoxia-stimulated glucose uptake in GLUT4-deficient muscles by muscle-specific GLUT4 transgenic complementation. *J Biol Chem*. 1998; 273:20910–20915.
147. **Zhang SJ, Sandström M, Ahlsén M, et al.** 2-Methoxyoestradiol inhibits glucose transport in rodent skeletal muscle. *Exp Physiol*. 2010;95:892–898.
148. **Mu J, Brozinick JT Jr, Valladares O, Bucan M, Birnbaum MJ.** A role for AMP-activated protein kinase in contraction- and hypoxia-regulated glucose transport in skeletal muscle. *Mol Cell*. 2001;7:1085–1094.
149. **Lanner JT, Katz A, Tavi P, et al.** The role of Ca2+ influx for insulin-mediated glucose uptake in skeletal muscle. *Diabetes*. 2006;55:2077–2083.
150. **Azevedo JL Jr, Carey JO, Pories WJ, Morris PG, Dohm GL.** Hypoxia stimulates glucose transport in insulin-resistant human skeletal muscle. *Diabetes*. 1995;44:695–698.
151. **Ryder JW, Yang J, Galuska D, et al.** Use of a novel impermeable biotinylated photolabeling reagent to assess insulin- and hypoxia-stimulated cell surface GLUT4 content in skeletal muscle from type 2 diabetic patients. *Diabetes*. 2000;49:647–654.
152. **Idström JP, Rennie MJ, Scherstén T, Bylund-Fellenius AC.** Membrane transport in relation to net uptake of glucose in the perfused rat hindlimb. Stimulatory effect of insulin, hypoxia and contractile activity. *Biochem J*. 1986;233: 131–137.
153. **Gamboa JL, Garcia-Cazarin ML, Andrade FH.** Chronic hypoxia increases insulin-stimulated glucose uptake in mouse soleus muscle. *Am J Physiol Regul Integr Comp Physiol*. 2011;300:R85–R91.
154. **Heinonen I, Kemppainen J, Kaskinoro K, et al.** Effects of adenosine, exercise, and moderate acute hypoxia on energy substrate utilization of human skeletal muscle. *Am J Physiol Regul Integr Comp Physiol*. 2012;302:R385–R390.
155. **Katz A, Sahlin K.** Effect of hypoxia on glucose metabolism in human skeletal muscle during exercise. *Acta Physiol Scand*. 1989;136:377–382.
156. **Zhang JZ, Behrooz A, Ismail-Beigi F.** Regulation of glucose transport by hypoxia. *Am J Kidney Dis*. 1999;34: 189–202.
157. **Fujii N, Jessen N, Goodyear LJ.** AMP-activated protein kinase and the regulation of glucose transport. *Am J Physiol Endocrinol Metab*. 2006;291:E867–E877.
158. **Zierath JR, Krook A, Wallberg-Henriksson H.** Insulin action and insulin resistance in human skeletal muscle. *Diabetologia*. 2000;43:821–835.
159. **Brozinick JT Jr, Reynolds TH, Dean D, Cartee G, Cushman SW.** 1-[N, O-bis-(5-isoquinolinesulphonyl)-N-methyl-L-tyrosyl]-4- phenylpiperazine (KN-62), an inhibitor of calcium-dependent camodulin protein kinase II, inhibits both insulin- and hypoxia-stimulated glucose transport in skeletal muscle. *Biochem J*. 1999;339:533–540.
160. **Fazakerley DJ, Lawrence SP, Lizunov VA, Cushman SW, Holman GD.** A common trafficking route for GLUT4 in cardiomyocytes in response to insulin, contraction and energy-status signalling. *J Cell Sci*. 2009;122:727–734.
161. **Xia Y, Warshaw JB, Haddad GG.** Effect of chronic hypoxia on glucose transporters in heart and skeletal muscle of immature and adult rats. *Am J Physiol*. 1997;273:R1734–R1741.
162. **Han XX, Bonen A.** Epinephrine translocates GLUT-4 but inhibits insulin-stimulated glucose transport in rat muscle. *Am J Physiol*. 1998;274:E700–E707.
163. **Nielsen JN, Jørgensen SB, Frøsig C, et al.** A possible role for AMP-activated protein kinase in exercise-induced glucose utilization: insights from humans and transgenic animals. *Biochem Soc Trans*. 2003;31:186–190.
164. **Dinmore AJ, Edwards JS, Menzies IS, Travis SP.** Intestinal carbohydrate absorption and permeability at high altitude (5,730 m). *J Appl Physiol*. 1994;76:1903–1907.
165. **Boyer SJ, Blume FD.** Weight loss and changes in body composition at high altitude. *J Appl Physiol*. 1984;57: 1580–1585.
166. **Kayser B, Acheson K, Decombaz J, Fern E, Cerretelli P.** Protein absorption and energy digestibility at high altitude. *J Appl Physiol*. 1992;73:2425–2431.
167. **Chesner IM, Small NA, Dykes PW.** Intestinal absorption at high altitude. *Postgrad Med J*. 1987;63:173–175.
168. **Sridharan K, Malhotra MS, Upadhayay TN, Grover SK, Dua GL.** Changes in gastro-intestinal function in humans at an altitude of 3,500 m. *Eur J Appl Physiol*. 1982;50: 145–154.
169. **Shukla V, Singh SN, Vats P, Singh VK, Singh SB, Banerjee PK.** Ghrelin and leptin levels of sojourners and acclimatized lowlanders at high altitude. *Nutr Neurosci*. 2005;8: 161–165.
170. **Wasse LK, Sunderland C, King JA, Batterham RL, Stensel DJ.** Influence of rest and exercise at a simulated altitude of 4,000 m on appetite, energy intake, and plasma concentrations of acylated ghrelin and peptide YY. *J Appl Physiol*. 2012;112:552–559.
171. **Riepl RL, Fischer R, Hautmann H, et al.** Influence of acute exposure to high altitude on basal and postprandial plasma levels of gastroenteropancreatic peptides. *PLoS One*. 2012;7:e44445.
172. **Aeberli I, Erb A, Spliethoff K, et al.** Disturbed eating at high altitude: influence of food preferences, acute mountain sickness and satiation hormones. *Eur J Nutr*. 2013;52: 625–635.
173. **Ahrén B.** The future of incretin-based therapy: novel avenues–novel targets. *Diabetes Obes Metab*. 2011;13(suppl 1):158–166.
174. **Cummings DE, Overduin J.** Gastrointestinal regulation of food intake. *J Clin Invest*. 2007;117:13–23.
175. **Snyder EM, Carr RD, Deacon CF, Johnson BD.** Overnight hypoxic exposure and glucagon-like peptide-1 and leptin levels in humans. *Appl Physiol Nutr Metab*. 2008;33:929–935.
176. **Debevec T, Simpson EJ, Macdonald IA, Eiken O, Mekjavic IB.** Exercise training during normobaric hypoxic confinement does not alter hormonal appetite regulation. *PLoS One*. 2014;9:e98874.
177. **Staehr P, Hother-Nielsen O, Landau BR, Chandramouli V, Holst JJ, Beck-Nielsen H.** Effects of free fatty acids per se

on glucose production, gluconeogenesis, and glycogenolysis. *Diabetes*. 2003;52:260–267.
178. **Raynaud J, Drouet L, Martineaud JP, Bordachar J, Coudert J, Durand J.** Time course of plasma growth hormone during exercise in humans at altitude. *J Appl Physiol*. 1981; 50:229–233.
179. **Bergouignan A, Gozansky WS, Barry DW, et al.** Increasing dietary fat elicits similar changes in fat oxidation and markers of muscle oxidative capacity in lean and obese humans. *PLoS One*. 2012;7:e30164.
180. **Hojlund K, Wildner-Christensen M, Eshøj O, et al.** Reference intervals for glucose, β-cell polypeptides, and counterregulatory factors during prolonged fasting. *Am J Physiol Endocrinol Metab*. 2001;280:E50–E58.
181. **Zambon A, Hashimoto SI, Brunzell JD.** Analysis of techniques to obtain plasma for measurement of levels of free fatty acids. *J Lipid Res*. 1993;34:1021–1028.
182. **Boden G.** Obesity, insulin resistance and free fatty acids. *Curr Opin Endocrinol Diabetes Obes*. 2011;18:139–143.
183. **Ahima RS.** Adipose tissue as an endocrine organ. *Obesity*. 2006;14:242S–249S.
184. **Turer AT, Scherer PE.** Adiponectin: mechanistic insights and clinical implications. *Diabetologia*. 2012;55:2319–2326.
185. **Smith JD, Cianflone K, Martin J, Poirier P, Broderick TL, Noël M.** Plasma adipokine and hormone changes in mountaineers on ascent to 5300 meters. *Wilderness Environ Med*. 2011;22:107–114.
186. **Barnholt KE, Hoffman AR, Rock PB, et al.** Endocrine responses to acute and chronic high-altitude exposure (4,300 meters): modulating effects of caloric restriction. *Am J Physiol Endocrinol Metab*. 2006;290:E1078–E1088.
187. **Yi X, Liang Y, Huerta-Sanchez E, et al.** Sequencing of 50 human exomes reveals adaptation to high altitude. *Science*. 2010;329:75–78.
188. **Scheinfeldt LB, Soi S, Thompson S, et al.** Genetic adaptation to high altitude in the Ethiopian highlands. *Genome Biol*. 2012;13:R1.
189. **Semenza GL, Prabhakar NR.** The role of hypoxia-inducible factors in oxygen sensing by the carotid body. *Adv Exp Med Biol*. 2012;758:1–5.
190. **Semenza GL.** Oxygen sensing, homeostasis, and disease. *N Engl J Med*. 2011;365:537–547.
191. **Greer SN, Metcalf JL, Wang Y, Ohh M.** The updated biology of hypoxia-inducible factor. *EMBO J*. 2012;31: 2448–2460.
192. **Loboda A, Jozkowicz A, Dulak J.** HIF-1 and HIF-2 transcription factors–similar but not identical. *Mol Cells*. 2010;29:435–442.
193. **Gelfi C, De Palma S, Ripamonti M, et al.** New aspects of altitude adaptation in Tibetans: a proteomic approach. *FASEB J*. 2004;18:612–614.
194. **Hochachka PW.** Mechanism and evolution of hypoxia-tolerance in humans. *J Exp Biol*. 1998;201:1243–1254.
195. **Hochachka PW, Beatty CL, Burelle Y, Trump ME, McKenzie DC, Matheson GO.** The lactate paradox in human high-altitude physiological performance. *News Physiol Sci*. 2002;17:122–126.
196. **Viganò A, Ripamonti M, De Palma S, et al.** Proteins modulation in human skeletal muscle in the early phase of adaptation to hypobaric hypoxia. *Proteomics*. 2008;8: 4668–4679.
197. **Levett DZ, Radford EJ, Menassa DA, et al.** Acclimatization of skeletal muscle mitochondria to high-altitude hypoxia during an ascent of Everest. *FASEB J*. 2012;26:1431–1441.
198. **Palmer BF, Clegg DJ.** Ascent to altitude as a weight loss method: the good and bad of hypoxia inducible factor activation. *Obesity (Silver Spring)*. 2014;22:311–317.
199. **van Patot MC, Gassmann M.** Hypoxia: adapting to high altitude by mutating EPAS-1, the gene encoding HIF-2α. *High Alt Med Biol*. 2011;12:157–167.
200. **Stauss HM.** Baroreceptor reflex function. *Am J Physiol Regul Integr Comp Physiol*. 2002;283:R284–R286.
201. **Zoll J, Ponsot E, Dufour S, et al.** Exercise training in normobaric hypoxia in endurance runners. III. Muscular adjustments of selected gene transcripts. *J Appl Physiol*. 2006;100:1258–1266.
202. **Lima GA, Anhê GF, Giannocco G, Nunes MT, Correa-Giannella ML, Machado UF.** Contractile activity per se induces transcriptional activation of SLC2A4 gene in soleus muscle: involvement of MEF2D, HIF-1a, and TRα transcriptional factors. *Am J Physiol Endocrinol Metab*. 2009;296:E132–E138.
203. **Sakagami H, Makino Y, Mizumoto K, et al.** Loss of HIF-1α impairs GLUT4 translocation and glucose uptake by the skeletal muscle cells. *Am J Physiol Endocrinol Metab*. 2014;306:E1065–E1076.
204. **McClain DA, Abuelgasim KA, Nouraie M, et al.** Decreased serum glucose and glycosylated hemoglobin levels in patients with Chuvash polycythemia: a role for HIF in glucose metabolism. *J Mol Med (Berl)*. 2013;91:59–67.
205. **Solís J, Guerra-García R.** Prevalence of diabetes mellitus in hospitalized patients from highlands [in Spanish]. *Arch Biol Andina*. 1979;9:21–30.
206. **Singh I, Chohan IS, Lal M, et al.** Effects of high altitude stay on the incidence of common diseases in man. *Int J Biometeorol*. 1977;21:93–122.
207. **Seclén S, Leey J, Villena A, et al.** Prevalence of obesity, diabetes mellitus, arterial hypertension, and hypercholesterolemia as risk factors for coronary and cerebrovascular diseases in adult populations from the coast, mountain and the forest in Peru [in Spanish]. *Acta Méd Per*. 1999;17:8–12.
208. **Woolcott OO, Castillo OA, Gutierrez C, Elashoff RM, Stefanovski D, Bergman RN.** Inverse association between diabetes and altitude: a cross-sectional study in the adult population of the United States. *Obesity (Silver Spring)*. 2014;22:2080–2090.
209. **Field AE, Coakley EH, Must A, et al.** Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med*. 2001;161:1581–1586.
210. **Bonora E, Kiechl S, Willeit J, et al.** Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes*. 2004;53:1782–1789.
211. **Woolcott OO, Castillo OA, Bergman RN.** Overweight and obesity in dwellers from highlands [in Spanish]. *Rev Peru Epidemiol*. 2012;16:5.
212. **Segura-Vega L, Agusti R, Parodi-Ramirez J.** Risk factors of

cardiovascular diseases in Peru (TORNASOL study)[in Spanish]. *Rev Peru Cardiol*. 2006;32:82–128.
213. **Sherpa LY, Deji, Stigum H, Chongsuvivatwong V, Thelle DS, Bjertness E.** Obesity in Tibetans aged 30–70 living at different altitudes under the north and south faces of Mt. Everest. *Int J Environ Res Public Health*. 2010;7:1670–1680.
214. **Voss JD, Allison DB, Webber BJ, Otto JL, Clark LL.** Lower obesity rate during residence at high altitude among a military population with frequent migration: a quasi experimental model for investigating spatial causation. *PLoS One*. 2014;9:e93493.
215. **Medina J, Morey OL, Zea H, et al.** Prevalence of overweight and obesity in an adult population from Greater Arequipa: outcomes from the PREVENCION study [in Spanish]. *Rev Peru Cardiol*. 2006;32:194–209.
216. **Málaga G, Zevallos-Palacios C, Lazo Mde L, Huayanay C.** High frequency of dyslipidemia and impaired fasting glycemia in a high altitude Peruvian population [in Spanish]. *Rev Peru Med Exp Salud Publica*. 2010;27:557–561.
217. **Mohanna S, Baracco R, Seclén S.** Lipid profile, waist circumference, and body mass index in a high altitude population. *High Alt Med Biol*. 2006;7:245–255.
218. **Shah SM, Nanan D, Rahbar MH, Rahim M, Nowshad G.** Assessing obesity and overweight in a high mountain Pakistani population. *Trop Med Int Health*. 2004;9:526–532.
219. **Schargrodsky H, Hernández-Hernández R, Champagne BM, et al.** CARMELA: assessment of cardiovascular risk in seven Latin American cities. *Am J Med*. 2008;121:58–65.
220. **Negi PC, Bhardwaj R, Kandoria A, et al.** Epidemiological study of hypertension in natives of Spiti valley in Himalayas and impact of hypobaric hypoxemia; a cross-sectional study. *J Assoc Physicians India*. 2012;60:21–25.
221. **Chen W, Liu Q, Wang H, et al.** Prevalence and risk factors of chronic kidney disease: a population study in the Tibetan population. *Nephrol Dial Transplant*. 2011;26:1592–1599.
222. **Voss JD, Masuoka P, Webber BJ, Scher AI, Atkinson RL.** Association of elevation, urbanization and ambient temperature with obesity prevalence in the United States. *Int J Obes (Lond)*. 2013;37:1407–1412.
223. **Dipierri JE, Bejarano IF, Alfaro EL, et al.** Overweight and obesity prevalence in highlands populations of Jujuy province (Argentina). In: Nieto JL, Obon JA, Baena S, eds. *Genes, Environment, and Disease in Human Populations* [in Spanish]. Zaragoza, Spain: Prensas Universitarias de Zaragoza; 2008:521–530.
224. **Hirschler V, Maccallini G, Aranda C, Molinari C.** Dyslipidemia without obesity in indigenous Argentinean children living at high altitude. *J Pediatr*. 2012;161:646–651.e1.
225. **Khalid Mel-H.** Is high-altitude environment a risk factor for childhood overweight and obesity in Saudi Arabia? *Wilderness Environ Med*. 2008;19:157–163.
226. **Kayser B, Verges S.** Hypoxia, energy balance and obesity: from pathophysiological mechanisms to new treatment strategies. *Obes Rev*. 2013;14:579–592.
227. **Srivastava KK, Kumar R.** Human nutrition in cold and high terrestrial altitudes. *Int J Biometeorol*. 1992;36:10–13.
228. **Gill MB, Pugh LG.** Basal metabolism and respiration in men living at 5,800 m (19,000 ft). *J Appl Physiol*. 1964;19:949–954.
229. **Stock MJ, Norgan NG, Ferro-Luzzi A, Evans E.** Effect of altitude on dietary-induced thermogenesis at rest and during light exercise in man. *J Appl Physiol*. 1978;45:345–349.
230. **Hannon JP, Sudman DM.** Basal metabolic and cardiovascular function of women during altitude acclimatization. *J Appl Physiol*. 1973;34:471–477.
231. **Mawson JT, Braun B, Rock PB, Moore LG, Mazzeo R, Butterfield GE.** Women at altitude: energy requirement at 4,300 m. *J Appl Physiol*. 2000;88:272–281.
232. **Lippl FJ, Neubauer S, Schipfer S, et al.** Hypobaric hypoxia causes body weight reduction in obese subjects. *Obesity (Silver Spring)*. 2010;18:675–681.
233. **Leonard WR, Katzmarzyk PT, Stephen MA, Ross AG.** Comparison of the heart rate-monitoring and factorial methods: assessment of energy expenditure in highland and coastal Ecuadoreans. *Am J Clin Nutr*. 1995;61:1146–1152.
234. **Kashiwazaki H, Dejima Y, Orias-Rivera J, Coward WA.** Energy expenditure determined by the doubly labeled water method in Bolivian Aymara living in a high altitude agropastoral community. *Am J Clin Nutr*. 1995;62:901–910.
235. **Levine JA, Lanningham-Foster LM, McCrady SK, et al.** Interindividual variation in posture allocation: possible role in human obesity. *Science*. 2005;307:584–586.
236. **van Marken Lichtenbelt WD, Schrauwen P.** Implications of nonshivering thermogenesis for energy balance regulation in humans. *Am J Physiol Regul Integr Comp Physiol*. 2011;301:R285–R296.
237. **Basu M, Pal K, Malhotra AS, Prasad R, Sawhney RC.** Free and total thyroid hormones in humans at extreme altitude. *Int J Biometeorol*. 1995;39:17–21.
238. **Ramirez G, Herrera R, Pineda D, Bittle PA, Rabb HA, Bercu BB.** The effects of high altitude on hypothalamic-pituitary secretory dynamics in men. *Clin Endocrinol (Oxf)*. 1995;43:11–18.
239. **Antezana AM, Richalet JP, Noriega I, Galarza M, Antezana G.** Hormonal changes in normal and polycythemic high-altitude natives. *J Appl Physiol*. 1995;79:795–800.
240. **Dhar P, Sharma VK, Hota KB, et al.** Autonomic cardiovascular responses in acclimatized lowlanders on prolonged stay at high altitude: a longitudinal follow up study. *PLoS One*. 2014;9:e84274.
241. **Tschöp M, Strasburger CJ, Hartmann G, Biollaz J, Bärtsch P.** Raised leptin concentrations at high altitude associated with loss of appetite. *Lancet*. 1998;352:1119–1120.
242. **Vats P, Singh VK, Singh SN, Singh SB.** High altitude induced anorexia: effect of changes in leptin and oxidative stress levels. *Nutr Neurosci*. 2007;10:243–249.
243. **Woolcott OO, Castillo OA, Torres J, Damas L, Florentini E.** Serum leptin levels in dwellers from high altitude lands. *High Alt Med Biol*. 2002;3:245–246.
244. **Santos JL, Pérez-Bravo F, Albala C, Calvillán M, Carrasco E.** Plasma leptin and insulin levels in Aymara natives from Chile. *Ann Hum Biol*. 2000;27:271–279.
245. **Subramanian SV, Finlay JE, Neuman M.** Global trends in body-mass index. *Lancet*. 2011;377:1915–1916; author reply 1917–1918.

246. **Picon-Reategui E.** The food and nutrition of high-altitude populations. In: Baker PT, ed. *The Biology of High-Altitude Peoples*. Cambridge, UK: Cambridge University Press; 1978:219–249.
247. **Faeh D, Gutzwiller F, Bopp M.** Response to letters regarding article, "Lower Mortality from Coronary Heart Disease and Stroke at Higher Altitudes in Switzerland". *Circulation*. 2010;121:e378.
248. **Posadas-Romero C, Yamamoto-Kimura L, Lerman-Garber I, et al.** The prevalence of NIDDM and associated coronary risk factors in Mexico City. *Diabetes Care*. 1994; 17:1441–1448.
249. **Al-Habori M, Al-Mamari M, Al-Meeri A.** Type II diabetes mellitus and impaired glucose tolerance in Yemen: prevalence, associated metabolic changes and risk factors. *Diabetes Res Clin Pract*. 2004;65:275–281.
250. **Faeh D, Gutzwiller F, Bopp M.** Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation*. 2009;120:495–501.
251. **Burke JP, Williams K, Haffner SM, Villalpando CG, Stern MP.** Elevated incidence of type 2 diabetes in San Antonio, Texas, compared with that of Mexico City, Mexico. *Diabetes Care*. 2001;24:1573–1578.
252. **Tai K, Need AG, Horowitz M, Chapman IM.** Vitamin D, glucose, insulin, and insulin sensitivity. *Nutrition*. 2008; 24:279–285.
253. **Engelsen O.** The relationship between ultraviolet radiation exposure and vitamin D status. *Nutrients*. 2010;2:482–495.
254. **Simha V, Mahmood M, Ansari M, Spellman CW, Shah P.** Effect of vitamin D replacement on insulin sensitivity in subjects with vitamin D deficiency. *J Investig Med*. 2012; 60:1214–1218.
255. **Seida JC, Mitri J, Colmers IN, et al.** Clinical review: effect of vitamin D3 supplementation on improving glucose homeostasis and preventing diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;99:3551–3560.
256. **Pearson JF, Bachireddy C, Shyamprasad S, Goldfine AB, Brownstein JS.** Association between fine particulate matter and diabetes prevalence in the U.S. *Diabetes Care*. 2010; 33:2196–2201.
257. **Lee DH, Lee IK, Song K, et al.** A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care*. 2006;29:1638–1644.
258. **Bravo Alvarez H, Sosa Echeverria R, Sanchez Alvarez P, Krupa S.** Air quality standards for particulate matter (PM) at high altitude cities. *Environ Pollut*. 2013;173:255–256.
259. **DeFronzo RA.** Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am*. 2004;88:787–835, ix.
260. **Marquez JL, Rubinstein S, Fattor JA, Shah O, Hoffman AR, Friedlander AL.** Cyclic hypobaric hypoxia improves markers of glucose metabolism in middle-aged men. *High Alt Med Biol*. 2013;14:263–272.
261. **Aurora RN, Punjabi NM.** Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med*. 2013;1:329–338.
262. **Tasali E, Mokhlesi B, Van Cauter E.** Obstructive sleep apnea and type 2 diabetes: interacting epidemics. *Chest*. 2008;133:496–506.
263. **Niijima M, Kimura H, Edo H, et al.** Manifestation of pulmonary hypertension during REM sleep in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 1999; 159:1766–1772.
264. **Braun B, Butterfield GE, Dominick SB, et al.** Women at altitude: changes in carbohydrate metabolism at 4,300-m elevation and across the menstrual cycle. *J Appl Physiol*. 1998;85:1966–1973.
265. **Kelly KR, Williamson DL, Fealy CE, et al.** Acute altitude-induced hypoxia suppresses plasma glucose and leptin in healthy humans. *Metabolism*. 2010;59:200–205.
266. **Coste O, Van Beers P, Touitou Y.** Impact of hypobaric hypoxia in pressurized cabins of simulated long-distance flights on the 24 h patterns of biological variables, fatigue, and clinical status. *Chronobiol Int*. 2007;24:1139–1157.
267. **Meyer C, Nadkarni V, Stumvoll M, Gerich J.** Human kidney free fatty acid and glucose uptake: evidence for a renal glucose-fatty acid cycle. *Am J Physiol*. 1997;273:E650–E654.
268. **Khan AJ, Hussain H, Omer SB, et al.** High incidence of childhood pneumonia at high altitudes in Pakistan: a longitudinal cohort study. *Bull World Health Organ*. 2009; 87:193–199.