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Glucose Intolerance by Interaction between Hypoxia Adaptation and Lifestyle Change in Highlanders in Tibet Plateau

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Summary

Socioeconomic factors and hypoxia play major roles in the prevalence of glucose intolerance in highlanders. Hypoxemia and polycythemia were closely associated with glucose intolerance after adjustment for the effects of lifestyle changes in our study. Tibetan people may be vulnerable to glucose intolerance, with polycythemia as a sign of poor hypoxic adaptation. Epigenetics is also play a role in its vulnerability with quick lifestyle change. Prevention of lifestyle-related diseases and health education should be advocated, especially in high altitude dwellers with rapidly prevailing socioeconomic globalization.

Introduction

Over many generations, people living at high altitudes have developed unique practices to survive in challenging environments with limited ecological resources.[1–3] Traditionally, diabetes mellitus (DM) has been uncommon among highlanders[4,5] compared with lowlanders.[6,7] Lifestyle-related diseases, such as DM and hypertension, are rapidly increasing with an increase in longevity and changes in lifestyle worldwide. A remarkable increase in DM has been reported in lowlander and semi-high altitude (around 1300 m) migrants who moved from traditional lifestyles to Westernised lifestyles.[8–10] Prevention of DM has become an urgent issue among lowlanders, especially in developing countries, where the rate of DM prevalence is much faster than in developed countries.[11,12] Older people with a low economic status in rural areas might be vulnerable to impaired glucose tolerance or DM in developed and developing countries.[13,14] An adverse intrauterine environment is a risk factor of diabetes,[15] and there is an association between low birth weight and type 2 diabetes.[16] These phenomena all show adaptation to a low-caloric intake, and the rapid change to a high intake likely increases the risk of diabetes, possibly through a mechanism related to epigenetics.[17,18]

People living at high altitudes not only have the previously mentioned risk factors, but they are also subject to hypoxia in a severe natural environment.[19] High-altitude dwellers show long-term adaptation to harsh environment-induced hypoxia. Highlanders are biologically adapted to hypoxic environments by various genetic mechanisms, such as an increase in haemoglobin concentrations or increased blood flow without polycythemia.[20,21] Andean people have increased haemoglobin levels as a result of hypoxic adaptation, but they suffer from chronic mountain sickness with excessive polycythemia as a maladaptation to hypoxia more often than Tibetan people do.[22] Ageing, menopause, respiratory disorders, obesity and hypertension are risk factors of chronic mountain sickness.[23–26] As a result of rapid lifestyle changes related to urbanisation, highlanders are experiencing an alarming increase in diabetes.[27–30] Tibetan residents, especially those who are obese, may be more vulnerable to glucose intolerance[31] compared with Andean people.[5,32] Whether high-altitude dwellers are more vulnerable to diabetes as a result of lifestyle changes, compared with lowlanders, is unknown, but people living at high altitudes are known to be vulnerable to hypertension.[4,33–36]

A population-based study of the effects of high altitude, between 1200 and 3000 m, on the same ethnic group, showed a low prevalence of impaired glucose regulation at high altitudes.[37] Also, an inverse association has been shown between diabetes and altitudes lower than 3500 m in lowlanders.[38] Additionally, lowland patients with diabetes show better glucose intolerance improvement at a mildly high altitude.[39] However, there are no reports on whether dwelling at altitudes over 3500 m and hypoxemia increases the risk of diabetes. We previously reported a strong association between glucose intolerance and polycythemia in elderly Tibetan people living in two highland areas.[40] Because they had adapted to hypoxia by reducing polycythemia, polycythemia may be regarded as a sign of maladaptation to hypoxia for Tibetan people.

The aim of this study was to clarify the association of glucose intolerance with hypoxemia or dwelling at altitudes of 2900–4800 m in Tibetan highlanders, and to verify the hypothesis that high-altitude dwelling in Tibetan highlanders increases their vulnerability to DM when accelerated by lifestyle change or ageing. This hypothesis is based both on the current accelerated and modernised lifestyle change occurring in middle-aged and elderly highlanders coming from a traditional childhood lifestyle, and on the high prevalence of polycythemia in elderly Tibetan highlanders in contrast with younger Tibetans.

This paper is partly quoted from “J-curve association between glucose intolerance and hemoglobin and ferritin levels at high altitude”[41] and “Glucose intolerance associated with hypoxia in people living at high altitudes in the Tibetan highland”[42].

J-curve association between glucose intolerance and hemoglobin and ferritin levels at high altitude

A significant association between polycythemia and glucose intolerance and a J-curve association between glucose intolerance and hemoglobin and ferritin levels were found in highlanders.

Subjects comprised 285 farmers (106 male, 179 female; mean age 57.1 ± 11.0) in Domkhar (altitude 2,900–3800 m) and 215 nomads (112 male, 103 female; mean age 54.4 ± 10.8) in Changthang (3,900–4,900 m), Ladakh, India. The farmers were all local Ladakhis, and the nomads were 126 local Ladakhis and 89 Tibetan migrants from China.

Hyperglycemia was defined according to the World Health Organization guidelines as oral glucose tolerance test results indicating diabetes mellitus (DM) and intermediate hyperglycemia (IHG).[40,43] Subjects were classified according to hemoglobin level as having anemia (male <13.0 g/dL, female <12.0 g/dL), normal hemoglobin (male 13.0–17.9 g/dL, female 12.0–15.9 g/dL), moderate polycythemia (MPC) (male 18.0–20.9 g/dL, female 16.0–18.9 g/dL), and excessive polycythemia (EPC) (male ≥21.0 g/dL, female ≥19 g/dL). Ferritin levels were classified as low (≤25 ng/mL), normal (male 25.0–299.9 ng/mL, female 25.0–149.9 ng/mL), and high (male ≥300 ng/mL, female ≥150 ng/mL).[44]

Men were more likely to have EPC and high ferritin (19.3 ng/mL, 40.8%) than women (6.4 ng/mL, 16.7%), and women were more likely to have anemia and low ferritin (19.1 ng/mL, 41.8%) than men (2.3 ng/mL, 7.8%).

Multiple logistic regression analysis showed the association between hemoglobin level and hyperglycemia (IHG and DM) adjusted for sex, blood oxygen saturation, body mass index (BMI), and lifestyle (farmer vs nomad) (Model 1). Anemia and polycythemia were associated with hyperglycemia (Table 1). The J-curve association was remarkable in the analysis of women (n=282), with a prevalence of IHG/DM of 24.1%/3.7% in those with anemia (odds ratio (OR)=3.08 (95% confidence interval (CI)=1.33–7.12), 22.4%/9.4% in those with MPC (OR=3.35, 95% CI=1.62–6.94), and 27.8%/27.8% in those with EPC (OR=10.19, 95% CI=3.04–34.16) compared with those with normal hemoglobin (16.8%/0%).

Seven groups were classified according to hemoglobin and ferritin levels. Subjects with anemia were classified as having iron deficiency anemia (IDA) (ferritin <12.0 ng/mL) or non-IDA (ferritin ≥12.0 ng/mL); those with normal hemoglobin were classified as having low, normal, or high ferritin; and those with MPC and EPC were not classified according to ferritin level because most had normal or high ferritin.

Model 2 shows the association between the seven hemoglobin and ferritin groups and hyperglycemia adjusted for the same confounding factors. Subjects with normal hemoglobin and low ferritin had the lowest prevalence of hyperglycemia (reference group). The IDA group was associated with hyperglycemia. Subjects with high ferritin and normal hemoglobin had a tendency toward hyperglycemia. Subjects with MPC and EPC were much more likely to have hyperglycemia (Table 1). This association between hyperglycemia and the combination of high ferritin and polycythemia was remarkable in men (n=218; normal hemoglobin with high ferritin, OR=6.47, 95% CI=1.09–38.26; MPC, OR=11.64, 95% CI=2.06–65.72; EPC, OR=13.50, 95% CI=2.27–80.47).

Subjects with high hemoglobin and high ferritin (especially men) were more likely to have hyperglycemia. IDA was associated with hyperglycemia in all subjects (especially women).

Two hypotheses are proposed for the association between polycythemia and glucose intolerance. First, glucose intolerance under hypoxic stress causes microvascular complications leading to polycythemia as a compensatory response. Second, people with polycythemia may be susceptible to glucose intolerance, suggesting poorer adaptation to hypoxia than in those without.

A close association between high ferritin and glucose intolerance has been reported in lowland-dwelling individuals,[44,45] which is consistent with these findings. An association between anemia and DM in lowlanders has also been reported.[42,46,47] Renal insufficiency as a complication of DM or chronic inflammation is thought to induce normocytic anemia.[42,46] The association between IDA and glucose intolerance has been reported, although it is unclear whether the relationship is causal.[46,47] In the current study, 78.0% of anemia was IDA. IDA was associated with higher rates of hyperglycemia (23.9% IHG and 4.3% DM) than in the reference group, suggesting a lower prevalence of renal insufficiency as a complication.

In previous studies of hemoglobin levels in lowlanders,[43,48-50] multiple logistic regression analysis showed that anemia was not associated with glucose intolerance adjusted for age, sex and BMI, with the exception of the survey in Tosa (Japan),[43] where anemia was associated with low risk of hyperglycemia (OR=0.42, 95% CI=0.24–0.71).

In hypoxic environments, polycythemia and anemia may exacerbate hypoxic stress and increase susceptibility to glucose intolerance. Iron overload in polycythemia with high oxidative stress may accelerate this effect.[44] Further studies are required to fully elucidate the association between glucose intolerance not only with oxidative stress, but also with hypoxia-adaptive genes associated with low hemoglobin concentrations in Tibetan highlanders.[51]

Table 1　J-Curve Association of Hemoglobin and Ferritin Levels with Glucose Intolerance at High Altitude Adjusted for Related Variables Using Multiple Logistic Regression Analysis

Variable	All (Male/Female), n	IHG/DM, %	Model 1	Model 2
			Odds Ratio (95% Confidence Interval	
Age				
40–49	171 (72/99)	21.6/4.7	Reference	Reference
50–59	142 (60/82)	15.5/9.2	0.87 (0.50–1.50)	0.85 (0.49–1.50)
60–69	116 (45/71)	30.2/10.3	2.15(1.24–3.72)[c]	2.09 (1.18–3.68)[b]
≥70	71 (41/ 30)	29.6/8.5	1.53 (0.81–2.90)	1.46 (0.76–2.82)
Sex				
Female	(282)	20.6/5.3	Reference	Reference
Male	(218)	26.1/11.0	2.15 (1.24–3.72)[c]	2.03 (1.28–3.22)[c]
Blood oxygen saturation				
≥89%	327 (136/191)	24.2/6.1	Reference	Reference
<89%	173 (82/91)	20.8/11.0	1.19 (0.75–1.90)	1.18 (0.74–1.88)
BMI, kg/m^2				
<25.0	402 (178, 224)	22.1/6.5	Reference	Reference
≥25.0	98 (40, 58)	26.5/13.3	2.06 (1.25–3.37)[c]	1.94 (1.17–3.22)[c]
Lifestyle				
Nomad	215 (112/103)	16.7/7.4	Reference	Reference
Farmer	285 (106/179)	27.7/8.1	3.46 (2.08–5.77)[d]	3.74 (2.16–6.46)[d]
Hemoglobin level				
Anemia	59 (5/54)	25.4/3.4	2.39 (1.17–4.90)[b]	-
Normal	240 (115/125)	22.1/2.5	Reference	-
Moderate polycythemia	141 (56/85)	23.4/12.8	3.01 (1.78–5.06)[d]	-
Excessive polycythemia	60 (42/18)	23.3/21.7	4.76 (2.37–9.55)[d]	-
Hemoglobin and ferritin levels				
Anemia			-	
IDA	46 (2/44)	23.9/4.3	-	3.29 (1.25–8.63)[b]
Non-IDA	13 (3/10)	30.8/0	-	2.27 (0.56–9.22)
Normal hemoglobin				
Low ferritin	70 (13/57)	15.7/0	-	Reference
Normal ferritin	124 (68/56)	23.4/2.4	-	1.14 (0.50–2.56)
High ferritin	46 (34/12)	28.3/6.5	-	2.49 (0.93–6.70)[a]
Moderate polycythemia	141 (56/85)	23.4/12.8	-	4.01 (1.81–8.86)[d]
Excessive polycythemia	60 (42/18)	23.3/21.7	-	6.63 (2.60–16.90)[d]

All subjects in each group are assigned according to age, sex, blood oxygen saturation, body mass index (BMI), lifestyle, hemoglobin level, and hemoglobin and ferritin levels. The prevalence of intermediate hyperglycemia (IHG; fasting glucose 110–126 mg/dL or 140 2-hour glucose 140–200 mg/dL and diabetes mellitus (DM; fasting blood glucose >126 mg/dL or 2-hour blood glucose > 200 mg/dL) is shown for all subjects in each group.

Multiple logistic regression analysis of the association between hemoglobin levels and hyperglycemia (IHG and DM) (Model 1) and between seven groups of hemoglobin and ferritin levels and hyperglycemia (Model 2) adjusted for age, sex, hypoxia (blood oxygen saturation <89%), overweight (BMI ≥25.0 kg/m^2), and lifestyle (farmer vs nomad).

P < [a].10, [b].05, [c].01, [d].001.

IDA=iron-deficiency anemia (ferritin ≤12 ng/mL).

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Glucose intolerance associated with hypoxia in people living at high altitudes in the Tibetan highland

To clarify the association between glucose intolerance and high altitudes (2900–4800 m) in a hypoxic environment in Tibetan highlanders and to verify the hypothesis that high altitude dwelling increases vulnerability to diabetes mellitus (DM) accelerated by lifestyle change or ageing.

Cross-sectional epidemiological study was carried out on Tibetan highlanders. We enrolled 1258 participants aged 40–87 years. The rural population comprised farmers in Domkhar (altitude 2900–3800 m) and nomads in Haiyan (3000–3100 m), Ryuho (4400 m) and Changthang (4300–4800 m). Urban area participants were from Leh (3300 m) and Jiegu (3700 m).

Participants were classified into six glucose tolerance-based groups: DM, intermediate hyperglycaemia (IHG), normoglycaemia (NG), fasting DM, fasting IHG and fasting NG. Prevalence of glucose intolerance was compared in farmers, nomads and urban dwellers. Effects of dwelling at high altitude or hypoxia on glucose intolerance were analysed with the confounding factors of age, sex, obesity, lipids, haemoglobin, hypertension and lifestyle, using multiple logistic regression.

The prevalence of DM (fasting DM)/IHG (fasting IHG) was 8.9% (6.5%)/25.1% (12.7%), respectively, in all participants. This prevalence was higher in urban dwellers (9.5% (7.1%)/28.5% (11.7%)) and in farmers (8.5% (6.1%)/28.5% (18.3%)) compared with nomads (8.2% (5.7%)/15.7% (9.7%)) ($p=0.0140/0.0001$). Dwelling at high altitude was significantly associated with fasting IHG+fasting DM/fasting DM (ORs for >4500 and 3500–4499 m were 3.59/4.36 and 2.07/1.76 vs <3500 m, respectively). After adjusting for lifestyle change, hypoxemia and polycythemia were closely associated with glucose intolerance (Table 2).

Socioeconomic factors, hypoxemia and the effects of altitudes >3500 m play a major role in the high prevalence of glucose intolerance in highlanders. Tibetan highlanders may be vulnerable to glucose intolerance, with polycythemia as a sign of poor hypoxic adaptation, accelerated by lifestyle change and ageing.

Factors of "Epigenetics" in vulnerability to glucose intolerance in Ladakhi farmers

We compared the insulin secretion ability and resistance in Tibetan and Ladakhi people and discussed the interaction of hypoxia adaptation and lifestyle change to glucose intolerance.

Insulin secretion ability (HOMA-β) and insulin resistance (HOMA-R) were compared between 182 Tibetan urban people (average 60 years old) (Yushu, 3700 m) and 279 Ladakhi farmers (57 years old) (Domkhal, 2900 - 3800 m) and those relationship with lifestyle factors (obesity, hyperlipidemia) and glucose intolerance were examined.

The frequency of fasting hyperglycemia (FBS> 110 mg/dL) in Ladakhi farmers at 3800 m (104 people) (L) was equivalent (33% vs. 29%) to that of Tibetan urban people, despite the lower frequency of overweight (L vs T; 12% vs 67%) and hyperlipidemia (17% vs 64%) in Ladakhi compared with Tibetan. Ladakhi farmers' HOMA - R of NGT / IGT / DM was 0.6 / 0.9 / 1.5, and those were lower than 1.8 / 2.7 / 3.8 in Tibetan urban people. Ladakhi farmers' HOMA -β of NGT / IGT / DM was 30.3/ 24.5/ 18.9, and those were lower than 77.5/85.4/48.9 in Tibetan urban people.

It was suggested that Ladakhi farmers could be vulnerable to glucose intolerance due to lifestyle change compared to Tibetan urban people. As a reason for this, together with the low ability of adaptation to hypoxia, it is suggested that the decrease in insulin secretion ability may be related. As a background for this, the malnutrition status in childhood of Ladakhi farmers (factors of Epigenetics) was inferred.

Hypothesised associations of hypoxemia, polycythemia and glucose intolerance with the influence of ageing and lifestyle change (Figure 1).

Socioeconomic factors and hypoxia—the effect of altitudes over 3500 m—play major roles in the prevalence of glucose intolerance in highlanders. Hypoxemia and polycythemia were closely associated

Table 2 Associations of high-altitude, hypoxemia, and polycythemia with glucose intolerance adjusted for all other confounders by multiple logistic regression analysis

	Fasting hyperglycemia			Fasting DM			Hyperglycemia (OGTT)			DM (OGTT)		
	Odds ratio	Confidence interval	P	**Odds ratio**	Confidence interval	P	**Odds ratio**	Confidence interval	P	**Odds ratio**	Confidence interval	P
Age (years)												
40–49	Reference			Reference			Reference			Reference		
50–59	1.21	(0.77 to 1.91)	ns	1.49	(0.73 to 3.06)	ns	1.05	(0.73 to 1.52)	ns	1.73	(0.91 to 3.30)	0.0951
60–69	2.03	(1.34 to 3.07)	0.0008	2.06	(1.06 to 4.02)	0.0336	1.73	(1.23 to 2.43)	0.0016	2.34	(1.28 to 4.27)	0.0057
70+	1.36	(0.83 to 2.22)	ns	1.38	(0.62 to 3.06)	ns	1.79	(1.21 to 2.65)	0.0035	1.77	(0.89 to 3.54)	ns
Male (vs female)	2.17	(1.57 to 2.99)	<0.0001	2.5	(1.50 to 4.18)	0.0004	1.68	(1.29 to 2.18)	0.0001	1.95	(1.26 to 3.01)	0.0026
Overweight	1.68	(1.18 to 2.40)	0.0041	1.43	(0.82 to 2.52)	ns	1.66	(1.25 to 2.21)	0.0004	1.46	(0.91 to 2.35)	ns
Dyslipidemia	1.59	(1.14 to 2.22)	0.0058	2.11	(1.26 to 3.54)	0.0048	1.38	(1.05 to 1.81)	0.023	2.51	(1.60 to 3.92)	<0.0001
Hypertension	1.09	(0.78 to 1.50)	ns	1.18	(0.71 to 1.96)	ns	1.16	(0.88 to 1.51)	ns	1.26	(0.82 to 1.95)	ns
Livelihood												
Farmer	6.62	(3.56 to 12.32)	<0.0001	5.61	(1.90 to 16.55)	0.0018	3.83	(2.38 to 6.15)	<0.0001	3.10	(1.40 to 6.86)	0.0051
Nomad	Reference			Reference			Reference			Reference		
Urban dweller	2.53	(1.42 to 4.49)	0.0015	3.47	(1.28 to 9.42)	0.0145	2.66	(1.74 to 4.07)	<0.0001	1.96	(0.96 to 3.99)	0.0641
Altitude level												
2500–3499 m	Reference			Reference			Reference			Reference	1	
3500–4499 m	2.07	(1.44 to 2.98)	<0.0001	1.76	(0.94 to 3.28)	0.0767	1.23	(0.92 to 1.64)	ns	1.08	(0.65 to 1.78)	ns
4500+ m	3.59	(1.75 to 7.37)	0.0005	4.36	(1.33 to 14.31)	0.0150	1.25	(0.70 to 2.23)	ns	1.46	(0.59 to 3.65)	ns
Hypoxemia												
SpO_2 < 89%	1.48	(1.04 to 2.10)	0.0305	1.56	(0.92 to 2.65)	0.099	1.45	(1.07 to 1.97)	0.0183	1.72	(1.09 to 2.73)	0.0202
Group according to Hb												
Anemia	1.47	(0.75 to 2.89)	ns	0.95	(0.21 to 4.24)	ns	1.24	(0.74 to 2.08)	ns	0.84	(0.25 to 2.89)	ns
Normal	Reference			Reference			Reference			Reference		
Moderate polycythemia	2.00	(1.39 to 2.87)	0.0002	2.57	(1.44 to 4.60)	0.0014	1.90	(1.40 to 2.58)	<0.0001	2.34	(1.42 to 3.84)	0.0008
Excessive polycythemia	3.58	(2.11 to 6.06)	<0.0001	5.46	(2.62 to 11.38)	<0.0001	3.16	(1.94 to 5.15)	<0.0001	5.35	(2.76 to 10.34)	<0.0001

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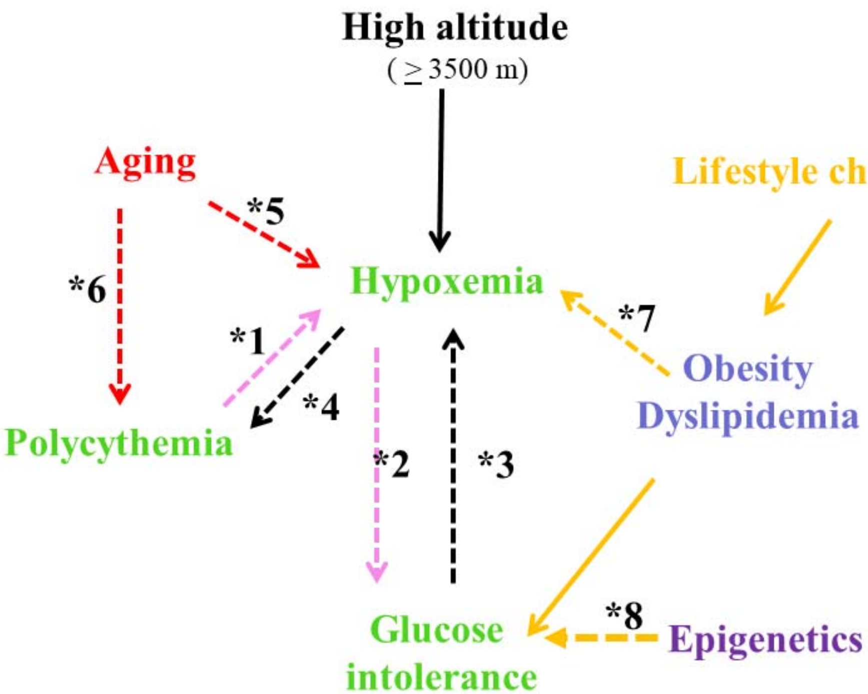
with glucose intolerance after adjustment for the effects of lifestyle changes in our study. Tibetan people may be vulnerable to glucose intolerance, with polycythemia as a sign of poor hypoxic adaptation. Epigenetics is also play a role in its vulnerability with quick lifestyle change.

However, the mechanism of the onset of glucose intolerance by hypoxemia in high altitude dwellers is unknown. A previous report showed higher oxidative stress in Tibetan people compared with Han people, and higher oxidative stress was associated with glucose intolerance and arteriosclerosis.[52,53] Further examination of the metabolic mechanism and oxidative stress in association with the effects of genes involved in hypoxia adaptation in high altitude dwellers is needed. Because it has not been established that WHO criteria of glucose intolerance can be applicable in high-altitude people, the prognosis of Fasting HG and HG associated with high-altitude should be examined longitudinally. Prevention of lifestyle-related diseases and health education should be advocated, especially in high altitude dwellers with rapidly prevailing socioeconomic globalization.

Figure 1 Hypothesis in the association of hypoxia, polycythemia and glucose intolerance. Aging and lifestyle change accelerate the association, “*Diabetes acceleration hypothesis*”.



*1 or 4: Proposed according to our data.[42]
*2 or 3: Proposed according to our data [42] and previous studies (references 54–60).
*1 and *2: Proposed according to a previous study (reference 61).
*3 and *4: Proposed according to previous studies (references 62 and 63).
*5: Proposed according to our data.[42]
*6: Proposed according to our data[42] compared with a previous study (reference 64).
*7: Proposed according to our data.[42]
*8: Proposed according to this report.
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付記）

2017年6月2日—4日にわたり、信州大学第一内科・花岡正幸教授会長のもとに、松本において開催された第4回アジア・太平洋登山医学会において、「ヒマラヤ学誌」編集委員の奥宮清人博士の演題が、一般演題101題のなかからThe Best Paper Award（最優秀賞）を受賞した。その経緯を付記する。

受賞のテーマと研究の内容

奥宮演題は、「Glucose intolerance by interaction between hypoxia adaptation and lifestyle change in Tibetan Plateau（チベット高地住民の耐糖能異常に関する生理学的高所適応性と生活習慣の変化に関する研究）」。

内容は、奥宮博士が約8年間にわたり、リーダーとして主導した総合地球環境学研究所プロジェクト「人の生老病死と高所環境—「高地文明」における医学・生態・文化的適応」から得られた所見の一端を示すものであった。

従来、高所医学研究というと、通常は平地に住む私たち登山家がヒマラヤなどの高所に登ったときに体内でどのような生理学的変化をおこすか、すなわち「高所順応（High Altitude Acclimatization）」の問題が主題であった。しかし、奥宮プロジェクト研究の卓越すべき観点は、約1万年以上前から高所（3－4千メートル）に適応したと考えられる高地住民の「高所適応（High Altitude Adaptation）」と老化が、最近のグロバリゼーションによる生活変化とどのように関連するのかという進化の過程を視野に入れる斬新なものであった。

世界の三大高地して、(1) アンデス、(2) チベット・ヒマラヤ、(3) エチオピア高地が知られている。長い進化の過程で現生人類の祖先がチンパンジーの祖先と分岐したのは、約700万年前のアフリカと考えて間違いないと思われるが、考古学的推測からも、現生人類が高地に達したのは、エチオピア高地が最も古く約10万年前、チベット・ヒマラヤに達したのは3－4万年前、アンデス高地に人類が住みはじめたのは約1万年くらい前と推測されている。ところが、低酸素環境である高地に適応する人体の生理学的機序は、エチオピア高地住民とチベット・ヒマラヤ高地住民、アンデス高地住民の3地域では異なるらしいという証拠が、21世紀になってから示された。ただ、高所適応の機序は、化石には残らないので、あくまで仮説の段階である。この問題に、「老化と耐糖能異常」という医学的ツールを導入して、正面から取り組んだのが奥宮プロジェクトであった。

「人類の高所適応」に関する20世紀後半の研究によって、アンデス高地住民では酸素を運搬するヘモグロビンを増やすことによって低酸素に適応し、チベット高地住民ではヘモグロビンを増やすことなく血管を拡張させ血流を増やすことによって高地適応しているのではないか、エチオピアでは詳細不明、という研究結果が示された。若年—壮年者のヘモグロビン値を3高地で比較した研究によると、アンデス高地住民が一番高く、次にチベット高地住民、エチオピア高地住民では平地住民と変わらない数値であるという結果である。

私たち通常は平地に住む登山家が、ヒマラヤ高所に登るとまずヘモグロビンが急激に上昇することは、1990年の京都大学ヒマラヤ医学学術登山隊の実測によって確認されているが、現在の平地住民の高所適応はアンデス型ともいえる。進化的時間軸から考えると、“つい最近”高地に達したのはアンデス高地住民ですので、私たち平地人の遺伝子設計もそのようになっているようである。

この学会にも参加していた、米国のCase Western Reserve UniversityのCynthia Beal教授という女性研究者は、チベット高地住民の高所適応に関する遺伝人類学的研究をライフワークとしてきた著名な学者で、ご主人もチベット学の研究者である。奥宮プロジェクトでは、Beal教授を何度も日本に招聘し議論を重ねてきた。このBeal教授のグループが最近、多くのチベット高地住民では、ヘモグロビン上昇を抑制する遺伝子変異があることを実証し、この遺伝子変異が高所適応のキーではないかという説を提唱した。とくにチベット族では、低酸素適応調節遺伝子のひとつE-PAS1という遺伝子の変異が、ヘモグロビンを上昇させない機能をもっていることが推測されている。

なお近年、考古遺伝学的な研究から、この低酸素適応遺伝子変異の起源は、約40万年前にアルタイ山脈のデニソワ洞窟で発見されたいわゆるデニソワ人に起因する可能性が指摘された。デニソワ人とは、ネアンデルタール人と近縁なグループ

で、約80万年前に、現生人類の共通祖先からネアンデルタール・デニソワ人の祖先が分岐し、64万—35年前にネアンデルタール人から分岐した人類であると推測されている。アジア内陸部でデニソワ人と交雑した現生人類の祖先の一部が、高地に移動しチベット高所民族となった可能性がでてきている。

奥宮研究グループは、中国青海省、アンデス高地、エチオピア高地在住高齢者の比較医学的な研究を行い、チベット高齢者では必ずしもヘモグロビンの上昇が抑制されていないケースが存在することを明らかにした。同時に、ヘモグロビンが高いチベット高齢者では、耐糖能異常（糖尿病もしくはその前段階）が多いことも発見した。考察として、低酸素適応に有利に作用した遺伝子発現の威力は、人生50 − 60歳くらいまでは有効だが、チベット人も社会環境の変化によって高齢まで生存できるようになり、また経済·社会環境のグローバル化による生活習慣の変化ともあいまって、本来、ヘモグロビンの上昇をおさえるEPAS-1遺伝子変異の威力がepigenetics（加齢と環境による遺伝子発現の修飾）過程を経て変化しつつある可能性を示した。そして奥宮演題の問題提起は、従来、若・壮年者を対象とする過去の人類学的な調査をもとに得られた結論も、高地も含めてグローバルに進む長寿と近年の生活習慣の変化によって、Trade-Offのような現象がおきつつあるのではないかという仮説提唱である。斯界に大きな影響を与えている。

受賞にいたる経緯

アジア太平洋登山医学会では、座長推薦とあらかじめ表彰審査員が数名指名され分担して、全演題をサーチし、各審査員の推挙演題を認定審査会で審議・決定する仕組みになっている。奥宮研究は、総合地球環境学研究所をバックとして大きな研究予算と研究時間に恵まれて、チベット、アンデス、エチオピア在住高齢者に関する8年間にわたる地域間比較医学研究、研究地域規模の壮大性、医学研究グループがたんねんに現地で調査したのち解析・議論して出した実証的な仮説、研究目的である「人類の進化的な高所適応」という過去の登山医学界では議論もされなかった新視点などを考えると、登山医学界に新領域を創出したといえる。

Pasha　インド登山医学会会長、Buddaネパール登山医学会会長、Ge Rili中国青海省登山医学会会長、米国Cynthia　Beal教授など、アジア太平洋登山医学会を率いる斯界で著名な外国人研究者も学会に出席していた。彼らは、今回の演題に限らず、世界の高所在住高齢者の老化に関する奥宮論文をよく熟知しており注目していたようである。とくに、Pashaインド登山医学会会長は、奥宮プロジェクトのカウンターパートとして京都の総合地球環境学研究所に半年間滞在したインド・ラダークの共同研究者ノルブー医師と友人らしく、学会終了後、奥宮率いる京都グルーを表敬したいとのことで来洛され2時間ほど懇談した。

奥宮演題の受賞は、登山医学の課題が、高所順化（High Altitude Acclimatization）から、高所適応（High Altitude Adaptation）へと拡大したあかしともいえる。「ヒマラヤ学誌」編集委員会としても、名誉と考え、巻頭論文として掲載させていただいた。

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