



Effects of lifestyle on plasma levels of the IGF system and the antioxidants coenzyme Q10 and vitamin E in Kenyan rural and urban populations

G. Theuri^a, G. Dallner^{b,c}, K. Brismar^b, M. Tekle^{b,c,*}

^a Kenyatta University, School of Applied Human Sciences, Department of Exercise Recreation and Sports Science, Nairobi, Kenya

^b Department of Molecular Medicine and Surgery, Karolinska Institutet, Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska University Hospital Stockholm, Sweden

^c Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden

ARTICLE INFO

Article history:

Received 27 June 2012

Received in revised form 10 January 2013

Accepted 14 January 2013

Available online 26 February 2013

Keywords:

Insulin-like growth factor-I

Insulin-like growth factor binding protein-1

Coenzyme Q

Vitamin E

ABSTRACT

Objective: Overnight fasting blood plasma insulin-like growth factor-I (IGF-I), insulin-like growth factor binding protein-1 (IGFBP-1), coenzyme Q10, (CoQ) vitamin E and plasma lipids were compared between a semi-nomadic Samburu population and relatively urbanized cohorts from Nairobi, Kenya.

Research design and methods: 143 middle aged subjects without known diabetes were included. IGF-I and IGFBP-1 were analyzed by RIA, and CoQ and vitamin E by HPLC. Plasma lipid levels were analyzed by standard laboratory methods routinely used in the clinics.

Results: The age adjusted IGF-I serum levels were low in the Samburu male and female populations, ranging from 0 to −4 IGFS-D-score (SDS), and a minor part of the investigated population reaching as low as −5 and −7 SDS. The Nairobi cohorts showed significantly higher values reaching from −2.5 to +1 SDS ($P < 0.0001$). The nomadic Samburu population showed fasting IGFBP-1 values ranging from 30–100 µg/l, while that of the urbanized Nairobi cohorts was considerably lower (25–60 µg/l) ($P < 0.0001$). CoQ concentrations of the Nairobi cohorts were 1.5–2.0 nmol/ml similar to the levels found in several European countries. The Samburu population on the other hand showed extremely high CoQ values ranging from 2 to 9 nmol/ml ($P < 0.0001$). Vitamin E levels of the Nairobi group were low (5–20 nmol/ml), but the Samburu population had even lower levels ranging from 3 to 15 nmol/ml ($P < 0.0001$). Plasma lipid levels such as cholesterol, triglycerides, LDL/HDL, ApoB/ApoA ratios as well as BMI and weight were significantly higher in the Nairobi population ($P < 0.0001$).

Conclusions: Low IGF-I and high IGFBP-1 levels of the Samburu cohorts indicate malnutrition. High lipid levels of the Nairobi cohorts indicate that these groups have several risk factors for cardiovascular diseases and diabetes type2.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Infections and nutritional deficiency related disorders predominate in populations of the developing countries. In the middle income countries, however, as nutritional situation improves and sedentary life style becomes more common, the infectious diseases are reduced and cardiovascular diseases are increasing. According to The World Health Organization Report 1999, non-communicable diseases and cardiovascular diseases are increasing in the middle income countries [1]. The high incidences of cardiovascular diseases, obesity, diabetes, dyslipidemia and hypertension

in the developing countries are linked by common lifestyle determinants such as diet, physical activity, as well as alcohol and tobacco consumptions [1]. The IGF system plays a significant role in normal growth and development as well as in several major diseases and pathologic states such as diabetes and cancer [2,3]. IGF-I is a peptide hormone mainly produced in the liver and its activity is regulated by IGFBP-1. IGFBP-1 facilitates the transport of IGF-I from plasma to tissues thus increasing the bioavailability and activity of IGF-I in the target tissues, but it may also have independent effects through interactions with cell surface molecules [4]. IGFBP-1 is an important determinant of IGF-I activity. IGFBP-1 is highly dependent on insulin concentrations and is found in higher concentrations in the serum during fasting and early mornings [5]. High levels of insulin are associated with low IGFBP-1 concentrations, and low levels of circulating IGFBP-1 are associated with the typical characteristics of metabolic syndromes such as insulin resistance, obesity and the development of cardiovascular diseases [2,6]. Serum levels of IGFBP-1 vary considerably in healthy individuals, 64% of which is attributed to non-genetic factors such as dietary and other environmental factors. On the other hand, IGF-I variations in healthy individuals could be ascribed to non-genetic factors by 35% [7].

Abbreviations: CoQ, Coenzyme Q10; IGF-I, Insulin-like growth factor-I; IGFBP-1, Insulin-like growth factor binding protein -1; LDL, Low density lipoprotein; HDL, High density lipoprotein; VLDL, Very low density lipoprotein; ApoA, Apolipoprotein A; ApoB, Apolipoprotein B; HPLC, High performance liquid chromatography; RIA, Radioimmunoassay.

* Corresponding author at: Department of Molecular Medicine and Surgery, Karolinska Institutet, Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska University Hospital Stockholm, Sweden. Tel.: +46 8 517 747 27; fax: +46 8 517 75 988.

E-mail address: michael.tekle@ki.se (M. Tekle).

Genetic and environmental factors independently determine the levels of coenzyme Q10 (CoQ), while the other major lipid soluble antioxidant, vitamin E originates from the diet. We have previously analyzed these substances in healthy females from three European countries with different nutritional habits. Significant differences in the IGF and antioxidant contents between the populations were observed [8]. CoQ and vitamin E are the main lipid-soluble antioxidants in the body involved in the protective mechanisms of neutralizing free radicals and reactive oxygen species that are present in the cells in abundance, not only as a result of toxic reagents from our environment, but also as a product of catabolic reactions under normal conditions [9]. Vitamin E is also important in a number of other metabolic functions such as stimulating the immune response, modulating protein kinase C and counteracting the conversion of nitrates to nitrosamines [10,11]. CoQ is a member of the mitochondrial respiratory chain, modulates the function of uncoupling proteins, regulates the mitochondrial permeability transition pool and activates the immune response of the monocytes [9].

The aim of this study was to explore and establish the association of the IGF-system and lipid-soluble antioxidants to the lifestyle of different ethnic groups and populations in the Southern hemisphere in order to find connections to the increasing number of pathological conditions such as the metabolic syndrome and cardiovascular diseases.

2. Materials and methods

2.1. Study populations

The population in this study was composed of 143 healthy individuals 30–60 years of age from two different regions in Kenya, an urban population from Nairobi and a semi-nomadic rural population from the district of Samburu in north central Kenya. The cohorts were composed of sixty nine individuals from Samburu (42 females and 27 males) and sixty seven from Nairobi (30 females and 37 males). The participants were healthy (self-reported) and not taking any medications. The protocol was approved by the ethical committee of the country. Age, weight and height were recorded for every participant and blood samples, 10 ml from each were collected in appropriate tubes after an overnight fasting. The samples were subsequently centrifuged at 2000 rpm for 5 min. The isolated plasma was immediately frozen at -20°C and later shipped on dry ice for analysis.

2.2. Inclusion and exclusion criteria

Subjects were eligible if they were between the ages of 30 to 60 years. Presentation of an identity card or passport was used to determine the age of subjects. Since among the Samburu, many were illiterate and did not know their age, the local field assistants estimated the age of the individuals by their groups or period in time when they underwent rites of passage like circumcision. Subjects were eligible if they had been residents in either area for five years prior to the start of the study for at least 90% of the time. Any history of pharmacological therapy for a cardiovascular disease, dyslipidemia, diabetes, recent infection, pregnancy as well as tobacco smoking within the past 12 months rendered the subjects ineligible.

2.3. IGF-I and IGFBP-1 analysis

IGF-I was analyzed by an in-house RIA after separating IGFs from IGFBPs by acid ethanol extraction and crayon-precipitation. To minimize interference of remaining IGFBPs, des (1-3) IGF-I tracer was used as radio-ligand [12]. The intra- and inter-assay coefficients of variation were 4% and 11%, respectively. Since serum levels of IGF-I are age dependent, and decrease with age, the IGF-I values were expressed as SD scores calculated from the age adjusted regression of the values of Swedish subjects with a total of 122 individuals between 20 and 60 years old, the gender distribution was 58 men and 64 women [13].

22% was in the third, 27% in the fourth, 30% in the fifth and 21% in the sixth decade of life.

The IGFBP-1 levels were measured by an in-house RIA according to the method of Póva et al. [14]. In each assay 50 μl plasma was incubated with antibody, and 10,000 cpm ^{125}I -npIGFBP-1 in a final volume of 300 μl in Tris-HCl assay buffer containing 1% bovine serum albumin. After overnight incubation at 4°C , bound counts were separated with goat anti-rabbit (SacCel, Boldon, England). The sensitivity of the RIA was 3 $\mu\text{g/l}$ and the intra- and inter-assay coefficients of variation were 3% and 10%, respectively.

2.4. HPLC analysis of CoQ and vitamin E

Vitamin E and CoQ were extracted from the samples according to Bentinger et al. [15] with some modifications. Plasma was thawed at room temperature and briefly centrifuged to sediment cell debris. 0.25 ml plasma plus 0.25 ml H_2O was mixed with 3 ml methanol and an internal standard of 0.5 nmol CoQ6 and 5 nmol Δ -tocopherol was added. The mixture was briefly vortexed and 1.2 ml petroleum-ether was added and shaken by hand for about 15 s. Finally, phase separation was attained by adding 2 ml methanol and 1.8 ml petroleum-ether and shaken again for another 15 s. Samples were then centrifuged for 2 min and the upper phase of petroleum ether was transferred to a new tube. The rest was re-extracted with 3 ml petroleum ether. Both upper phases were pooled and the sample was dried under a gentle stream of nitrogen and finally dissolved in chloroform: methanol (2:1) and analyzed by HPLC. HPLC analyses were performed on a Shimadzu (LC-10AD) using a Hypersil ODS 4.6×60 mm, 3.5 μm , C18 (Agilent Technologies) reversed-phase column with a Zorbax SB-C8 4.6×30 mm, 3.5 μm (Agilent Technologies) guard column. A linear gradient was used from the initial methanol/water, 9:1, in pump system A to methanol/2-propanol/hexane, 2:1:1, in pump system B, at a flow rate of 1.5 ml/min and with a program time of 30 min. Absorbance was monitored at 275 and 292 nm [16].

2.5. Lipid analysis

Total cholesterol concentrations were determined by spectrophotometer according to Allain CC et al. [17]. ApoA and ApoB were determined as described elsewhere [18]. HDL, LDL and triglyceride measurements were performed according to established methods described previously [19,20].

2.6. Statistical analysis

All results are expressed as mean values and within 95% confidence interval (CI). To evaluate whether there is any evidence that the means of the populations differ when comparing differences between females and males of the two population groups, one-way ANOVA was used. This was followed by Tukey's multiple comparison when there was difference between group means. Spearman (nonparametric) was applied for the correlation analyses and when comparing the two populations, student's *t*-test was used.

3. Results

3.1. IGF-I and IGFBP-1

In order to verify whether the age dependent decline of IGF-I also applies to the Kenyan population, correlation of age to IGF-I expressed in $\mu\text{g/l}$ is shown in Fig. 1, ($P < 0.0001$ and $r = -0.56$) for the Samburu population and ($P < 0.0001$ and $r = -0.48$) for the Nairobi cohorts. Clearly, there exists age related decline of IGF-I in the Kenyan population. The IGF-I levels of the Samburu cohorts expressed as SDS are shown in Fig. 2A. Both the male and female populations show values ranging from -1 to -5 SD-score. The Nairobi group (Fig. 2B) however,

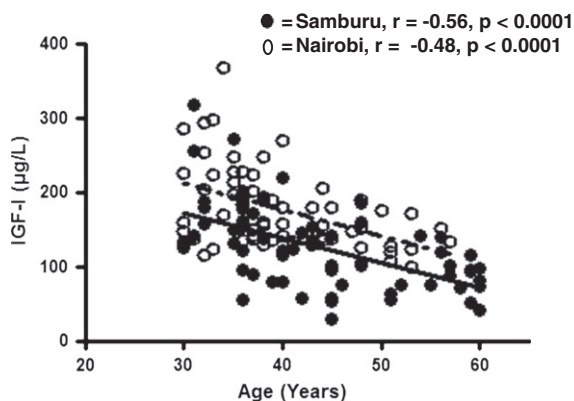


Fig. 1. Serum IGF-1 concentrations ($\mu\text{g/L}$) in relation to age (years). $P < 0.0001$ and $r = -0.56$ for Samburu and $P < 0.0001$ and $r = -0.48$ for Nairobi.

showed an SDS distribution of $+1$ to -2 which is significantly higher ($P < 0.0001$) than the Samburu cohorts and considered closer to the normal distribution values (0 SDS) as compared to the samples from Samburu. In the Samburu population, the IGFBP-1 values exhibited a broad range of distribution mainly from 10 – 110 $\mu\text{g/L}$ but some individuals had values exceeding 120 $\mu\text{g/L}$ (Fig. 2C) for both male and female groups. Most of the Nairobi cohorts have low IGFBP-1 concentrations ranging from 10 to 50 $\mu\text{g/L}$ (Fig. 2D). IGF-1 mean values were lower ($P < 0.0001$) in the Samburu populations of both genders than the Nairobi cohorts. However, IGFBP-1 mean values were higher ($P < 0.0001$) than that of the Nairobi cohorts (Table 2).

3.2. CoQ and vitamin E

The CoQ values were extremely high in the Samburu population ranging from 2 to 9 nmol/ml (Fig. 3A), while those of the urban population from Nairobi (1 – 2 nmol/ml) (Fig. 3B) are comparable to that published previously in a European population, with around 1 – 2 nmol/ml [8]. It should be noted that the two populations had relatively similar age distribution, as CoQ values are known to decrease during aging.

The rural population of Samburu, both female and male shows very low vitamin E levels ranging from 1 to 10 nmol/ml (Fig. 3C), while the Nairobi cohorts show higher levels (10 – 20 nmol/ml, $P < 0.0001$) (Fig. 3D) but significantly lower ($P < 0.0001$) compared to the values observed in previous measurements of European populations, ranging between 20 and 40 nmol/ml. The Nairobi cohorts had lower mean values of CoQ and higher vitamin E mean values than the Samburu population, (Table 2).

3.3. LDL and HDL

The HDL values of both populations were in the range of 1 – 2 mmol/l (Fig. 4A). There was a significant difference in HDL amount between the Samburu and Nairobi populations with the Nairobi cohorts having lower amounts ($P < 0.0005$) (Table 1). LDL concentrations were between 1.5 and 3.5 mmol/l in the Samburu population and between 1.5 – 4.5 mmol/l in the Nairobi groups (Fig. 4B). A significant difference is shown between the two populations, with the Samburu having lower levels compared to that of the Nairobi cohorts ($P < 0.0068$) (Table 1). The percentage distribution of LDL values higher than 3 mmol/l was 30% and 39% ($P < 0.0001$) for the females and 7% ($P < 0.05$) and 32% ($P < 0.0001$) for the males, from the Samburu and Nairobi groups respectively (not shown). We also calculated the LDL/HDL ratio (Fig. 4C and Table 1) as this is a predictor of coronary plaque formation and cardiovascular diseases. In the Samburu cohorts, the values were spread between ratios 1 and 3 for both the male and female groups. The ratios for the Nairobi groups varied from 1 to 4.5 , while the Samburu values for LDL/HDL ratio were significantly lower, ($P < 0.0001$). Only 3% ($P < 0.05$) of the Samburu population had LDL/HDL ratio above 3 , while in the Nairobi population, 23% ($P < 0.0001$) had LDL/HDL ratio exceeding 3 (not shown).

3.4. Apo A and Apo B

The ApoA levels were in the range of 1.5 – 3 g/l for all population groups without gender preferences (Fig. 5A). However, the mean values were significantly higher in the Samburu population ($p < 0.0001$). Likewise the ApoB values (Fig. 5B) were between 1 and 1.5 g/l in all groups

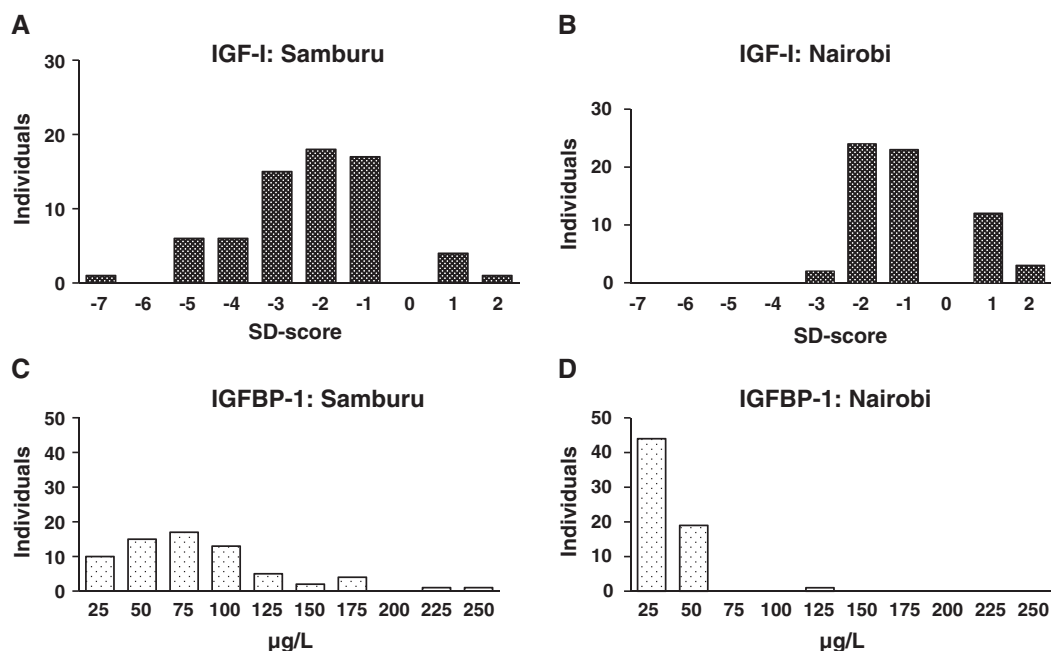


Fig. 2. IGF-1 SD-score levels in Samburu (A) and Nairobi (B) ($P < 0.0001$). IGFBP-1 ($\mu\text{g/L}$) serum levels of Samburu (C) and Nairobi (D) in the different Kenyan cohorts ($P < 0.0001$). IGFBP-1 values are grouped in intervals of 25 .

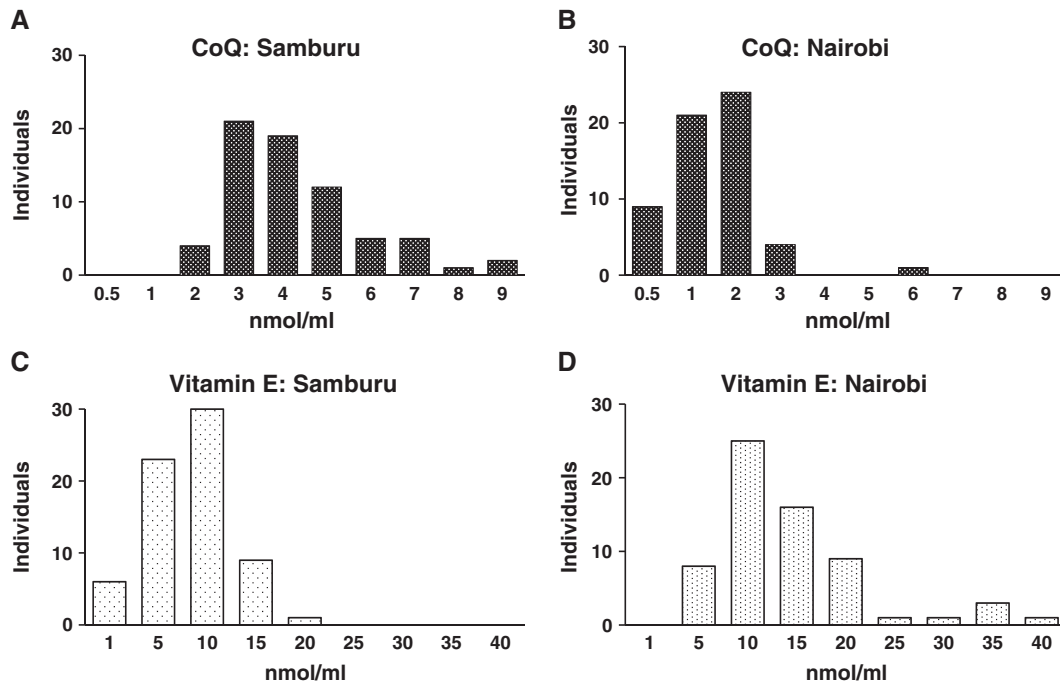


Fig. 3. CoQ serum levels (nmol/ml) in Kenyan populations: Samburu (A), Nairobi (B), vitamin E concentrations (nmol/ml) grouped in intervals of 5 are shown for Samburu (C) and Nairobi (D).

with significant differences between Samburu and Nairobi with the latter having higher values ($p < 0.0022$). The ApoB/ApoA ratio has been known to be associated with metabolic syndrome and insulin resistance and was therefore calculated (Fig. 5C and Table 1). The majority of the Samburu and Nairobi populations, both males and females had a distribution ratio of 0.5–0.75 with some ($P < 0.0001$) of the Nairobi females reaching up to ratio 1. Calculated in percent, 27% ($P < 0.0001$) of the males and 15% ($P < 0.0001$) of the females in Samburu had ratios exceeding 0.5. Ratios exceeding 0.5 are considered as indicators of insulin

resistance. In the Nairobi group, 31% ($P < 0.0001$) of the females and 60% ($P < 0.0001$) of the males had ApoB/ApoA ratio exceeding 0.5 (not shown). The ApoB/ApoA ratio correlation to IGFBP-1 concentrations is shown in (Fig. 5D), $r = -0.34$ and $p < 0.0001$.

3.5. Age, height, weight and BMI

Both population groups had a similar age pattern with the rural female group from Samburu (43.9 ± 9.51 , years) being slightly ($P < 0.041$)

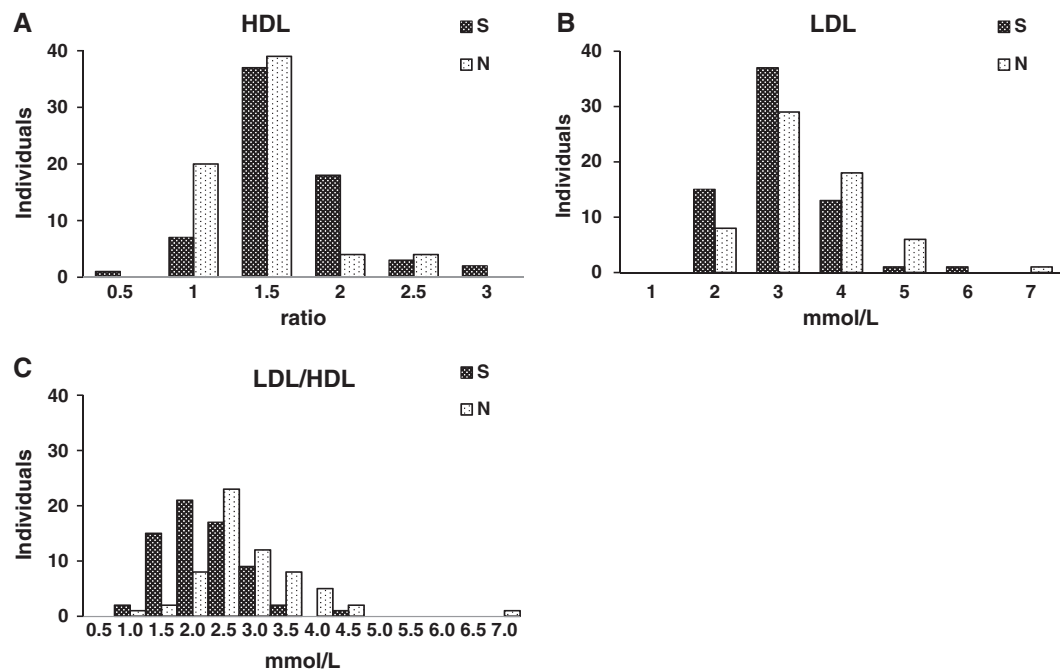


Fig. 4. Plasma levels of (A) HDL, (B) LDL (mmol/l) and (C) LDL/HDL ratio in the Samburu and Nairobi populations. Values are grouped in intervals of 0.5. S = Samburu and N = Nairobi.

Table 1
Clinical characteristics and physical features of the two populations, both females and males. Results are expressed as mean values \pm SD; ns = not significant; $P(S)$ and $P(N)$ = P-values when comparing females against males for both (S) Samburu and (N) Nairobi cohorts respectively; $All(S)$ and $All(N)$ = mean value of all participants in the (S) Samburu and (N) Nairobi groups respectively; $P(All)$ = P-values comparing the Samburu with the Nairobi groups.

	Samburu				Nairobi				
	Female	Male	$P(S)$	$All(S)$	Female	Male	$P(N)$	$All(N)$	$P(All)$
N	42	27		69	30	37		67	
Age (years)	43.9 \pm 9.5	42.0 \pm 9.6	Ns	43.2 \pm 9.53	41.7 \pm 7.0	38.5 \pm 6.7	ns	39.9 \pm 7.01	ns
Height (m)	1.63 \pm 0.05	1.77 \pm 0.08	<0.0001	1.68 \pm 0.09	1.61 \pm 0.06	1.74 \pm 0.09	<0.0001	1.68 \pm 0.10	ns
Weight (Kg)	53.2 \pm 13.7	54.4 \pm 13.0	Ns	53.6 \pm 13.3	67.9 \pm 11.1	78.7 \pm 11.5	<0.0003	73.9 \pm 12.5	<0.0001
BMI	19.9 \pm 4.6	17.4 \pm 4.2	<0.03	18.9 \pm 4.60	26.2 \pm 4.6	26.0 \pm 3.2	ns	26.1 \pm 3.85	<0.0001
HDL (mmol/l)	1.30 \pm 0.38	1.37 \pm 0.49	Ns	1.34 \pm 0.40	1.25 \pm 0.34	1.10 \pm 0.31	<0.005	1.12 \pm 0.34	<0.0002
LDL (mmol/l)	2.59 \pm 0.82	2.21 \pm 0.58	<0.04	2.44 \pm 0.75	2.95 \pm 0.75	2.79 \pm 1.0	ns	2.86 \pm 0.89	<0.0023
LDL/HDL	1.98 \pm 0.61	1.77 \pm 0.67	Ns	1.89 \pm 0.64	2.35 \pm 0.68	2.74 \pm 1.0	ns	2.56 \pm 0.88	<0.0001
Triglycerides (mmol/l)	1.29 \pm 0.71	1.22 \pm 0.61	Ns	1.26 \pm 0.67	1.56 \pm 1.21	2.17 \pm 1.15	<0.04	1.90 \pm 1.20	<0.0002
ApoB/ApoA	0.49 \pm 0.15	0.39 \pm 0.14	<0.01	0.45 \pm 0.16	0.51 \pm 0.19	0.62 \pm 0.19	<0.03	0.57 \pm 0.20	<0.0002
Cholesterol (mmol/l)	4.38 \pm 1.13	4.13 \pm 0.82	Ns	4.28 \pm 1.02	4.79 \pm 0.98	4.65 \pm 1.20	ns	4.71 \pm 1.10	<0.0219

older than those of Nairobi males (38.5 ± 6.74 , years) (Fig. 6A, B and Table 1). The height of the Samburu females (1.63 ± 0.05 , m) was similar to that of the Nairobi females (1.61 ± 0.05 , m) while that of the Samburu males (1.77 ± 0.08 m) was similar to their counter parts in the Nairobi male group (1.74 ± 0.09 m) (Fig. 6C, D and Table 1). There was a significant difference of weight between the Nairobi (73.3 ± 11.5 , kg) and Samburu (53.8 ± 13.5 kg) ($P < 0.0001$) populations both in males and females reflecting the standard of living of the groups (Fig. 7A and Table 1). Based on the height and weight parameters, the BMI (kg/m^2) for each group was calculated and there was a significant difference between the Nairobi (26.1 ± 3.9 kg/m^2) and Samburu (18.7 ± 4.4 kg/m^2) groups both in males and females ($P < 0.0001$) (Fig. 7B and Table 1). A log-transformed scatter plot correlation between body weight and IGFBP-1 (Fig. 7C) ($r = -0.73$, $p < 0.001$) and BMI and IGFBP-1 (Fig. 7D) ($r = -0.75$, $p < 0.0001$) was made showing inverse correlation. In Table 2, hormone and antioxidant levels of both Kenyan cohorts are

shown, and for comparison the Swedish values as representative for the European population, are also included.

3.6. Total cholesterol and triglycerides

Total cholesterol levels in the majority of the individuals were between 4 and 5 mmol/l (Table 1). This value is considered to be the upper limit in a European population. A significant amount of the females, 27% of the Samburu and 37% of the Nairobi had cholesterol concentrations exceeding 5 mmol/l ($P < 0.0001$), while for the male population it was lower, 7% (not significant) and 22% ($P < 0.0001$) respectively. The triglyceride levels of the Samburu female and male cohorts were significantly lower ($P < 0.0002$) than their Nairobi counterparts. Overall, the Samburu groups had values ranging between 1 and 2 mmol/l while those of the Nairobi had values between 1 and 3 mmol/l (Table 1). In the Samburu population the percentage of

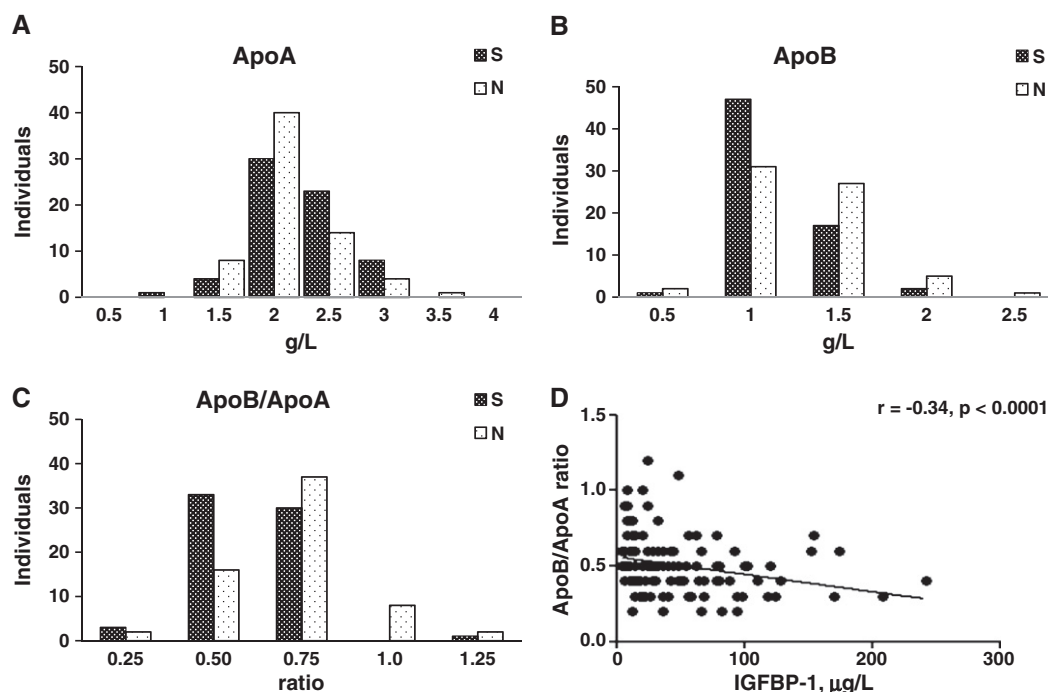


Fig. 5. ApoA (A), ApoB (B) concentrations (g/L), ApoB/ApoA ratio (C) and ApoB/ApoA ratio correlation to log IGFBP-1 (D) measured in the two Kenyan populations. Values are grouped in intervals of 0.5 for ApoA and ApoB and 0.25 for ApoB/ApoA ratio. S = Samburu and N = Nairobi.

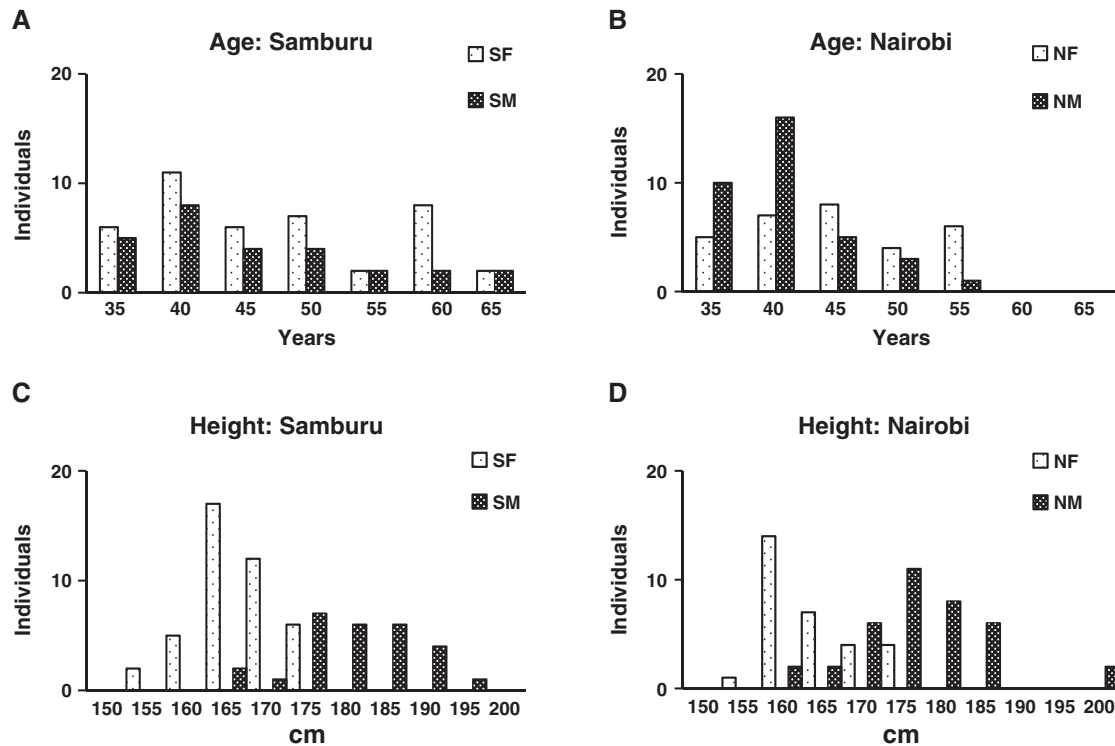


Fig. 6. Age of Samburu (A) and Nairobi (B) populations, height of the Samburu (C) and of the Nairobi groups (D). Values are grouped in intervals of 5 years where 35 include ages between 30 and 35 years. The height values are given in intervals of 5 cm where 150 cm represents those between 145 and 150 cm long. SF = Samburu females, SM = Samburu males, NF = Nairobi females and NM = Nairobi males.

males and females with triglyceride levels exceeding 1.8 mmol/l was 11% and 12% respectively ($P < 0.0001$). The percentage was considerably higher for both Nairobi groups reaching as high as 21% for females and 51% for the males ($P < 0.0001$).

4. Discussion

Both genetic and environmental factors are important determinants of the levels of circulating IGF-I and IGFBP-1 as well as of the antioxidant

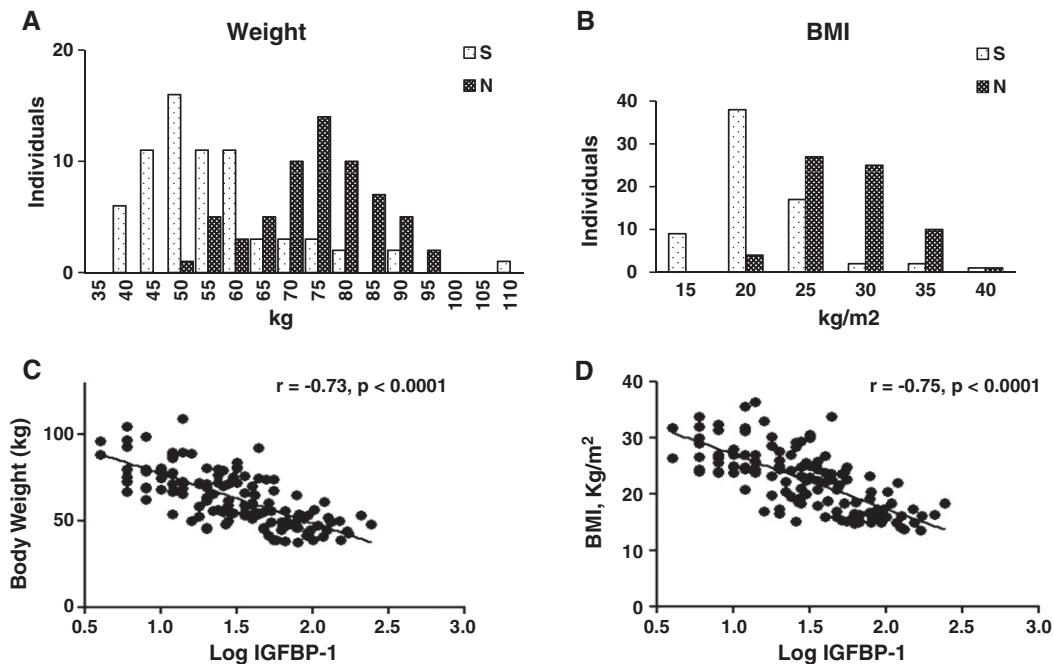


Fig. 7. The weight and BMI values of both populations. Weight in kg of both the Samburu and Nairobi populations grouped in intervals of 5 kg (A) and BMI (kg/m²) values of both cohorts grouped in intervals of 5 (B) are shown. Log transformed scatter plot correlation between body weight and log IGFBP-1 (C) $r = -0.73$, $p < 0.0001$; and between BMI and log IGFBP-1 (D) $r = -0.75$, $p < 0.0001$ are shown for all cohorts.

Table 2

Hormone and antioxidant levels in blood plasma values of the Samburu and Nairobi population are shown, and for comparison the Swedish values as representative for the European population, are also included. Results are expressed as mean values \pm SD. n = number of participants.

	Samburu	Nairobi	P	Sweden
N	69	67		122
IGF-I (SD-score)	-1.82 ± 1.46	-0.62 ± 0.87	<0.0001	0.07 ± 1.02
IGFBP-1 ($\mu\text{g/l}$)	68.8 ± 48.3	20.7 ± 15.5	<0.0001	27 ± 22.0
CoQ (nmol/ml)	3.79 ± 1.61	1.14 ± 0.81	<0.0001	0.98 ± 0.30
Vitamin E (nmol/ml)	5.76 ± 3.63	11.79 ± 7.60	<0.0001	23 ± 12.1

CoQ, while plasma levels of the lipid soluble antioxidant vitamin E are dependent on the nutritional status of the individual. We have previously analyzed these lipids in three European countries with different economic and nutritional habits where a significant difference in the IGF and antioxidant distribution between the populations was observed reflecting on how lifestyle and environmental factors affect these components. In this study we have investigated healthy female and male cohorts from two different regions of Kenya: an urban population from Nairobi and a rural population from the district of Samburu in north central Kenya. In the urban population of Nairobi, most of both genders have low amounts of IGFBP-1 indicating higher risk of developing insulin resistance and type 2 diabetes mellitus [4,11]. In addition these cohorts also have high cholesterol, triglycerides and LDL serum levels which are indicators of the risk of cardiovascular diseases and insulin resistance. In a recent study conducted on Asian Indian population, circulating IGFBP-1 amount was significantly lower in subjects who had insulin resistance compared with those without insulin resistance [21]. Subjects with diabetes mellitus had significantly lower IGFBP-1 levels when compared to those with normal glucose tolerance but with insulin resistance. The same study also shows that circulating IGFBP-1 levels decreased with increasing number of metabolic abnormalities which also seems to be the case in our study. However, a positive correlation between circulating IGFBP-1 levels and intima-media thickness was shown in a multivariate analyses study conducted on Caucasian men (with Apolipoprotein E3/E3 genotype) from the northern parts of the County of Stockholm [22]. Furthermore, there have been contradictory reports regarding IGFBP-1 and mortality. While, one report concluded that high serum IGFBP-1 concentration was related to increased risk for cardiovascular mortality irrespective of impaired glucose tolerance or diabetes [23], another study conducted on elderly men and women reports that low serum IGFBP-1 concentration was an independent risk factor for ischaemic heart disease and mortality [24]. In another cross-sectional population-based screening study that included 664 non-diabetic subjects aged 40–59, 12.6% of those with IGFBP-1 values less than $24 \mu\text{g/l}$ had developed type 2 diabetes, while the incidence was only 1.5% for those who had more than $59 \mu\text{g/l}$ [7]. Clearly, low levels of circulating IGFBP-1 are a marker of the metabolic syndrome and predict diabetes development [25–28]. The relatively higher serum lipids in the urban cohorts from Nairobi indicate that these populations have a higher risk for developing cardiovascular diseases and/or diabetes. The urban cohort of Nairobi is believed to have an increased dietary intake of carbohydrates and fats which could be one of the explanations for the low circulating IGFBP-1 levels in those groups. The low IGF-I and high IGFBP-1 levels in the plasma of the rural Samburu population indicate malnutrition and/or caloric restrictions compared to the relatively urbanized population of Nairobi which has near to normal IGF-I levels. However, malnutrition alone does not explain the low IGF-I status of the Samburu population since those groups were slightly taller than the urban cohorts, indicating that the reason for the low IGF-I levels is due to a reduced synthesis in the liver caused by genetic factors, protein deficiency or reduced insulin sensitivity. In fact this phenomenon has been observed in a study where Italian children aged 0.5–8 years were compared with children of the same age from the West African

nation of Ivory Coast [29]. Vitamin E derives from the diet, but its level in the blood is not dependent on the immediate dietary uptake since it is readily distributed by the liver into all parts of the body including the circulation where equilibrium is reached [30]. Vitamin E levels in the Samburu cohorts, both female and male are extremely low, about one third of the values published in European cohorts which are considered normal. This is apparently due to low consumption of vegetables which are good sources of vitamin E. In a number of individuals the amount was below 1 nmol/ml and in some it was not even detectable. It is possible that lipid mal-absorption or low lipid intake as well as defects in the lipid transporting proteins could contribute to the deficiency. On the other hand, the persons participating considered themselves healthy which may not support malfunctioning status. The vitamin E level of the Nairobi cohorts was in the lower normal range as compared to Polish and Swedish healthy female cohorts published earlier [8]. CoQ is the only endogenously synthesized lipid soluble antioxidant and despite the difference of their origin, it has been reported that CoQ and vitamin E increase and decrease simultaneously in most conditions [31]. In this study however, we report opposing concentration of these lipids, especially in the Samburu cohorts where the very low vitamin E levels are contrasted by the extremely high CoQ levels. It appears that the high CoQ level seen in this group could be a compensatory mechanism for the low vitamin E levels. Higher HDL and lower LDL and triglycerides in the Samburu cohort can be explained by the non-sedentary lifestyles of those populations [32].

Conflict of interest

The authors have nothing to declare.

Acknowledgments

The authors would like to thank Elvi Sandberg and Inga-Lena Wivall-Helleryd for their excellent technical assistance in performing the IGF-I and IGFBP-1 assays. We also like to thank Dr. Jing Wang for the statistical analysis and some of the figures. This work was supported by the Family Erling-Persson Foundation and the Swedish Research Council.

References

- [1] S. Yusuf, R. Srinath, S. Öunpuu, S. Anand, Global burden of cardiovascular diseases Part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization, *Circulation* 104 (2001) 2746–2753.
- [2] D.R. Clemmons, Modifying IGF1 activity: an approach to treat endocrine disorders, atherosclerosis and cancer, *Nat. Rev. Drug Discov.* 6 (2007) 821–833.
- [3] E. Giovannucci, Metabolic syndrome, hyperinsulinemia, and colon cancer, *Am. J. Clin. Nutr.* 86 (2007) S836–S842.
- [4] A. Bayes-Genis, C.A. Conover, R.S. Schwartz, The insulin-like growth factor axis: a review of atherosclerosis and restenosis, *Circ. Res.* 86 (2000) 125–130.
- [5] S. Yakar, H. Kim, H. Zhao, et al., The growth hormone insulin like growth factor axis revisited: lessons from IGF-1 and IGF-1 receptor gene targeting, *Pediatr. Nephrol.* 20 (2005) 251–254.
- [6] A. McDonald, R.M. Williams, F.M. Regan, R.K. Semple, D.B. Dunger, IGF-I treatment of insulin resistance, *Eur. J. Endocrinol.* 157 (2007) S51–S56.
- [7] U. Petersson, C.J. Östgren, L. Brudin, K. Brismar, P.M. Nilsson, Low levels of insulin-like growth-factor-binding protein-1 (IGFBP-1) are prospectively associated with the incidence of type 2 diabetes and impaired glucose tolerance (IGT): the Söderåkra Cardiovascular Risk Factor Study, *Diabetes Metab.* 35 (2009) 198–205.
- [8] M. Tekle, J. Gromadzinska, G. Joksic, et al., Plasma levels of insulin-like growth factor-I, insulin-like growth factor binding protein-1, coenzyme Q10 and vitamin E in female populations from Poland, Serbia and Sweden, *Environ. Int.* 36 (2010) 188–194.
- [9] M. Turunen, J. Olsson, G. Dallner, Metabolism and function of coenzyme Q, *Biochim. Biophys. Acta* 1660 (2004) 171–199.
- [10] A. Munteanu, J.M. Zingg, E. Orgu, et al., Modulation of cell proliferation and gene expression by alpha-tocopheryl phosphates: relevance to atherosclerosis and inflammation, *Biochem. Biophys. Res. Commun.* 318 (2004) 311–316.
- [11] J.M. Zingg, A. Azzi, Non-antioxidant activities of vitamin E, *Curr. Med. Chem.* 11 (2004) 1113–1133.
- [12] P. Bang, U. Eriksson, V. Sara, I.L. Wivall, K. Hall, Comparison of acid ethanol extraction and acid gel filtration prior to IGF-I and IGF-II radioimmunoassay: improvement of determinations in acid ethanol extracts by the use of truncated IGF-I as radio ligand, *Acta Endocrinol. (Copenh)* 124 (1991) 620–629.

- [13] A. Hilding, K. Brismar, M. Degerblad, M. Thorén, K. Hall, Altered relation between circulating levels of insulin-like growth factor binding protein-1 and insulin in growth hormone deficient patients and insulin-dependent diabetic patients compared to that in healthy subjects, *J. Clin. Endocrinol. Metab.* 80 (1995) 2646–2652.
- [14] G. Póva, A. Roovete, K. Hall, Cross-reaction of serum somatomedin-binding protein in a radioimmunoassay developed for somatomedin binding protein isolated from human amniotic fluid, *Acta Endocrinol.* 107 (1984) 563–570.
- [15] M. Bentinger, M. Turunen, X.X. Zhang, Y.J. Wan, G. Dallner, Involvement of retinoid X receptor alpha in coenzyme Q metabolism, *J. Mol. Biol.* 326 (2003) 795–803.
- [16] M. Tekle, M. Turunen, G. Dallner, T. Chojnacki, E. Swiezewska, Investigation of coenzyme Q biosynthesis in human fibroblast and HepG2 cells, *J. Biochem. Biophys. Methods* 70 (2008) 909–917.
- [17] C.C. Allain, L.S. Poon, C.S. Chan, W. Richmond, P.C. Fu, Enzymatic determination of total serum cholesterol, *Clin. Chem.* 20 (4) (1974) 470–475.
- [18] D. Brustolin, M. Maierna, F. Aguzzi, F. Zoppi, G. Tarengi, G. Berti, Immunoturbidimetric method for the routine determinations of apolipoproteins A-I and B, *Clin. Chem.* 37 (5) (1991) 742–747.
- [19] Y. Ueda, M. Matsui, S. Hayashi, Y. Yamaguchi, Y. Kanakura, New homogeneous HDL-cholesterol assay without the influence of high TG sample using the selective detergent to lipoproteins, *J. Clin. Lab. Anal.* 17 (2003) 201–208.
- [20] W.R. Lagor, D.W. Fields, S.A. Khetarpal, et al., The effects of Apolipoprotein F deficiency on high density lipoprotein cholesterol metabolism in mice, *PLoS One* 7 (2) (2012) 1–12.
- [21] K. Gokulakrishnan, K. Velmurugan, S. Ganesan, V. Mohan, Circulating levels of insulin-like growth factor binding protein-1 in relation to insulin resistance, type 2 diabetes mellitus, and metabolic syndrome (Chennai Urban Rural Epidemiology Study 118), *Metabolism* 61 (2012) 43–46.
- [22] S. Boquist, G. Ruotolo, C. Skoglund-Andersson, et al., Correlation of serum IGF-I and IGFBP-1 and -3 to cardiovascular risk indicators and early carotid atherosclerosis in healthy middle-aged men, *Clin. Endocrinol. (Oxf.)* 68 (1) (2008) 51–58.
- [23] M. Harrela, Q. Qiao, R. Koistinen, et al., High serum insulin-like growth factor binding protein-1 is associated with increased cardiovascular mortality in elderly men, *Horm. Metab. Res.* 34 (2002) 144–149.
- [24] G.A. Laughlin, E. Barrett-Connor, M.H. Criqui, D. Kritzer-Silverstein, The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study, *J. Clin. Endocrinol. Metab.* 89 (2004) 114–120.
- [25] M.S. Lewitt, A. Hilding, C.G. Östenson, S. Efendic, K. Brismar, K. Hall, Insulin-like growth factor-binding protein-1 in the prediction and development of type 2 diabetes in middle-aged Swedish men, *Diabetologia* 51 (7) (2008) 1135–1145.
- [26] M.S. Lewitt, A. Hilding, K. Brismar, S. Efendic, C.G. Östenson, K. Hall, IGF-binding protein 1 and abdominal obesity in the development of type 2 diabetes in women, *Eur. J. Endocrinol.* 163 (2) (2010) 233–242.
- [27] A.H. Heald, K.W. Siddals, W. Fraser, et al., Low circulating levels of insulin-like growth factor binding protein-1 (IGFBP-1) are closely associated with the presence of macrovascular disease and hypertension in type 2 diabetes, *Diabetes* 51 (2002) 2629–2636.
- [28] V. Mohamed-Ali, J.H. Pinkney, A. Panahloo, S. Cwyfan-Hughes, J.M. Holly, J.S. Yudkin, Insulin-like growth factor binding protein-1 in NIDDM: relationship with the insulin resistance syndrome, *Clin. Endocrinol. (Oxf.)* 50 (1999) 221–228.
- [29] M. Boschetti, D. Larizza, V. Calcaterra, et al., Effect of environment on growth: auxological and hormonal parameters in African and Italian children, *Growth Hormon. IGF Res.* 19 (2009) 238–241.
- [30] M.G. Taber, Vitamin E regulatory mechanisms, *Annu. Rev. Nutr.* 27 (2007) 347–362.
- [31] Y. Zhang, M. Turunen, E.L. Appelkvist, Restricted uptake of dietary coenzyme Q is in contrast to the unrestricted uptake of alpha-tocopherol into rat organs and cells, *J. Nutr.* 126 (1996) 2089–2097.
- [32] F.B. Hu, Sedentary lifestyle and risk of obesity and type 2 diabetes, *Lipids* 38 (2003) 103–108.