Soluble Transferrin receptors and Soluble Transferrin Receptor – Ferritin Index in a healthy African population of South Africa.

TANDI MATSHA [1*], LUCY T BRINK [2], SUSAN J VAN RENSBURG [2], RAJIV T ERASMUS [2]

[1] Department of Biomedical Sciences, Faculty of Health and Wellness Sciences, Cape Peninsula University of Technology, Cape Town.

[2] Department of Chemical Pathology, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, 7505.

* Dr Tandi E Matsha, Department of Biomedical Sciences, Faculty of Health & Wellness Sciences, Cape Peninsula University of Technology, P.O. Box 652, Cape Town 8000, South Africa
Tel: +27 21 460 3209 · Fax: +27 21 460 3193 · Email: matshat@cput.ac.za

Abstract

Background: South Africa has a high incidence of iron deficiency and HIV/Aids. The soluble transferrin receptor (sTfR) is not an acute phase reactant as is ferritin, hence it is useful for the diagnosis of iron deficiency in the presence of inflammation or infection.

Methods: To explore the use of sTfR and sTfR log ferritin index in evaluating body iron status, we measured soluble transferrin receptors and indirect measures of iron stores in 371 healthy Africans.

Results: We observed an inverse correlation between sTfR and log serum ferritin (r - 0.17, $P < 0.0001$), as well as sTfR log ferritin index and transferrin saturation (r - 0.26, $P < 0.0001$). Subjects classified as having iron deficiency (serum ferritin < 30µg/L and transferrin saturation < 15%) had significantly higher sTfR concentrations when compared to subjects with normal serum ferritin and transferrin saturation 15 50%, (9.2 ± 6.9µg/ml and 5.0 ± 2.4µg/ml, P < 0.0001) respectively. The concentrations of sTfR were normal to increased (5.5 ± 3.2 µg/ml) in subjects who may be classified as iron deficient based on serum ferritin levels (serum ferritin levels less than 30 µg/L, but transferrin saturation 15 50%). However, the sTfR log ferritin index was superior over sTfR values in differentiating between this group and subjects classified as normal, respectively, 4.6 ± 4.1 and 2.6 ± 1.2, P < 0.0001. No significant differences were observed between the iron overload group (serum ferritin raised) and normal subjects.

Conclusion: Based on these results we suggest that sTfR log ferritin index be used together with other parameters of iron stores in the diagnosis of iron deficiency, particularly when sTfR concentration results are equivocal.

Abbreviations:

TfR Transferrin receptor; Tf Transferrin; sTfR Soluble Transferrin receptor; IDA Iron deficiency anaemia; ACD Anaemia of chronic diseases; SF Serum ferritin; TS Transferrin saturation; TIBC Total iron binding capacity; CRP C-reactive protein; ALT Alanine Transaminase; SD Standard deviation; CI Confidence interval; Hb Haemoglobin; MCV Mean corpuscular volume

INTRODUCTION

The human transferrin receptor (TfR) is a homodimer of two identical transmembrane subunits, each of 84,910 Da and containing 760 amino acid residues that mediates uptake of iron from transferrin (Tf) (1) (2) (3) (4). Transferrin receptors are found in virtually all cells, except mature red cells. In normal adults, bone marrow expresses large amounts of TfR and is correspondingly competent in securing iron from Tf, while low receptor numbers are paralleled by reduced capacity to acquire iron bound to Tf (5). A soluble form of transferrin receptor (sTfR) which is derived from proteolytic cleavage of the extracellular segment (5) (6) (7) has been demonstrated in serum. (8). The sTfR levels are decreased in hypoplastic erythropoiesis and increased in erythroid hyperplasia, making measurement of sTfR an indicator erythropoietic activity (5) (10) (11) (12).

In the determination of body iron status, sTfR in conjunction with other conventional laboratory tests is used for the diagnosis of iron deficiency anaemia (IDA), particularly, in distinguishing IDA from anaemia of chronic diseases (ACD) (9) (13). The most frequently used conventional laboratory tests of iron status are serum ferritin (SF) and transferrin saturation (TS). Serum ferritin level is used as a marker of iron storage, and levels of less than 15µg/L are generally taken as indicating absent iron stores while a SF level of less than 30µg/L provides positive predictive values for IDA (14) (15). Serum ferritin levels greater than 200µg/L in females and 300µg/L in males are linked with iron overload (14). On the other hand, TS corresponds to the ratio of serum iron and total iron binding capacity (TIBC), therefore, it is influenced by the diurnal variations that affect serum iron. The overriding importance of TS is that a low value is useful in identifying anaemic individuals (16). It should be noted that TS remains the single indirect test used to screen for an iron-loading defect in HLA-linked hereditary haemachromatosis in Caucasians (17) (18). The disadvantage of SF and TS in the determination of body iron status is that in the presence of inflammation/infection SF values can be inappropriately increased whilst TS may be reduced (19) (20) (21) (22). In contrast, sTfR measurement is superior to these two tests as it is not influenced by acute phase proteins (5). Furthermore, the reciprocal relationship between sTfR and SF allows the combination of the two tests into a ratio of sTfR/ferritin or sTfR/log ferritin that has been shown to have excellent performance in estimating body iron stores (9).

Iron deficiency and iron overload are common problems in rural populations of Southern Africa (24) (25). Therefore, the objective of this study was to determine whether, as shown in other populations, sTfR concentrations or sTfR-log ferritin index can be used to assess body iron status in an African population of South Africa. We evaluated the relationship between sTfR concentration, sTfR log ferritin index and other biochemical parameters of iron status in a healthy rural African population.

MATERIALS AND METHODS

Ethics: The study was approved by the Ethics Committee of the University of Stellenbosch. Written informed consent was obtained from all participants, while the study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Study Population: Fasting venous blood samples were collected from 595 healthy African subjects with age ranging from 19 to 85 years from three rural villages of Transkei, South Africa. These subjects were a subset of individuals that consented to blood collection during 2003 to 2004 early screening programmes for oesophageal cancer by brush biopsy. On the day of collection all blood samples were centrifuged and serum stored at -20°C until analysis.

Analysis of blood samples: Serum iron, SF, serum transferrin (Tf), C-reactive protein (CRP) and Alanine Transaminase (ALT) concentrations were determined on a Cobas Mira auto-analyser using reagents from Cat Medicals, South Africa. The TS was calculated on the basis of Tf and serum iron concentrations as described by Tietz (26) (27). Briefly, Total iron binding capacity (TIBC) was calculated from Tf using Tietz's tables and percentage of TS was subsequently calculated as (serum iron/TIBC) X 100. Using this method and taking into account conversion of units, our routine laboratory has worked out that dividing serum iron (µmol/L) by the Tf (g/L) and multiplying by 3.989 determines transferrin saturation. Full Blood counts were determined on a Beckman Coulter auto-analyser using reagents from Beckman, South Africa. To differentiate between raised SF due to increased body iron stores versus alcohol-induced hepatocellular damage and inflammation, individuals with CRP values greater than 10mg/L and/or ALT greater than 40U/L were excluded. In the resulting subgroup (N 371), sTfR were measured in duplicate using an enzyme immunoassay Human Transferrin Receptor kit, (Ramco Laboratories, USA, Inc) as per manufacture's instructions. According to the manufacturer of the kit, the normal range for sTfR is 2.9 8.3µg/ml. sTfR log ferritin index was estimated with sTfR concentration / log SF.

***Statistical considerations*:** An Excel spreadsheet (Excel 2000, Microsoft Corp) and a statistics programme, STATISTICA (STATISTCA 7, StatSoft Inc 1984 2004) were used to perform all statistical analyses. Descriptive data are presented as enumerations, percentages or means and standard deviation (SD). Serum ferritin data are expressed as median and 95% confidence interval (CI). Correlations were calculated using Spearman's Rank correlation coefficient. For the purpose of describing variations of sTfR concentrations or sTfR- log SF index as a function of SF levels and/or TS, group means were

compared by ANOVA and post-hoc comparisons were performed by *Scheffe's test* at different breakpoints. Three breakpoints of SF levels were (IDA) SF < 30µg/L, (normal SF) 30 200µg/L for females and 30-300µg/L for males and (raised SF) > 200µg/L for females and > 300µg/L for males. The three breakpoints of TS % were (IDA) TS < 15%, TS 15 50% (normal TS) and TS > 50% (raised TS). The STATISTCA programme generated the following 8 breakpoints for the combination of SF and TS: (a) SF < 30ug/L plus TS < 15% (N 31), (b) normal SF plus TS 15 50% (N 202), (c) SF < 30ug/L plus TS 15 50% (N 51), (d) normal SF plus TS < 15% (N 35), (e) raised SF plus TS 15 - 50% (N 37), (f) raised SF and TS > 50% (N 4), (g) normal SF plus TS > 50% (N 5) and (h) raised SF plus TS < 15% (N 6). The latter 3 categories were not included in further statistical analysis due to their small numbers.

RESULTS

Using the exclusion criteria mentioned above, 224 subjects were excluded leaving a study population consisting of 76 males; age range 19 79, and 295 females; age range 19 85 years. The general baseline characteristics of the 371 control subjects are summarised according to sex in table 1. Soluble transferrin receptor concentrations were 4.9 ± 2.9 and 5.7 ± 3.3µg/ml in males and females, respectively, with no significant differences between the sexes. In order to analyse relationships between sTfR and indirect measurements of body iron stores, Spearman's Rank correlations were performed between sTfR and log of SF, TS, haemoglobin (Hb) and mean corpuscular volume (MCV). The results showed an inverse correlation between sTRF and log of SF, serum iron and TS, P < 0.0001 (Table 2).

Soluble transferrin ferritin index and sTfR concentrations in the different SF and TS breakpoints were analysed by ANOVA and are summarised in figures 1 and 2, respectively. In subjects with SF less than 30µg/L, sTfR values were 6.7 ± 4.8µg/ml (N 83) and these were statistically different from subjects with normal SF levels (N 242, 5.1 ± 2.5µg/ml, P < 0.0001). No statistically significant differences were observed between the group with raised SF levels and normal SF levels, P > 0.05 (Figure 1A). Figure 1B shows sTfR log ferritin Index in 371 subjects assigned to different categories of SF levels. In contrast to sTfR values, significant differences were observed between subjects with raised SF values and the group with SF levels < 30µg/L, respectively, 2.2 ± 1.3 and 5.7 ± 2.0, P < 0.0001). In subjects with TS < 15% (N 71) sTfR concentrations were significantly higher than in subjects with TS 15 50% (N 290), respectively, 7.33 ± 4.8µg/ml and 5.1 ± 2.6µg/ml, P < 0.0001. Similar to SF breakpoints, sTfR or sTfR-log ferritin index of subjects with raised TS were not significantly different from those of subjects with normal TS (Figure 2). Interestingly, the sTfR concentration of the normal groups, that is, TS 15 -50% or SF 30 -200ug/L (women) and 30 - 300ug/L (males) were similar (5.1 ± 2.6µg/ml and 5.1 ± 2.5µg/ml, respectively).

Variations of sTfR concentrations or sTfR-log ferritin index in 5 breakpoints of TS and serum SF levels are summarised in table 3. As determined by ANOVA and post-hoc comparison by *Scheffe's test,* sTfR or sTfR log ferritin index were significantly increased in the iron deficient group *(category a)* than the normal group *(category b),* sTfR 8.8 ± 6.5µg/ml and 5.0 ± 2.4µg/ml, P < 0.001; sTfR-log ferritin index 7.6 ± 5.8 and 2.6 ± 1.2, P < 0.0001, respectively. Interestingly, the sTfR concentrations of subjects with SF < 30µg/L but normal TS (15 50%) *(category c)* (5.4 ± 3.2µg/ml) were similar to those of subjects in the normal group *(category b)* (5.0 ± 2.4µg/ml), but significantly lower than the iron deficient group *(category a)* (8.8 ± 6.9 µg/ml), P < 0.0002. However, the sTfR log ferritin index of subjects with SF < 30µg/L but normal TS (15 50%) *(category c)* was significantly higher than that of subjects with normal SF plus normal TS *(category b),* P < 0.0001. sTfR concentrations of subjects with raised SF and TS 15 50% *(category e)* were normal to increased, but not significantly different, P > 0.05.

DISCUSSION

In the present study we provide evidence that sTfR are inversely and significantly proportional to indirect measures of the body iron stores (SF, TS) and that the sTfR concentrations of healthy Africans from a rural population of South Africa are similar to previously published observations (5). The mean sTfR concentration in a subgroup (N 202, table 3, category b) of the study population with normal SF levels and normal TS was slightly lower than that of the assay used (5.55 ± 1.35µg/ml), but similar to that reported by Beguin et al (5) in a group of 165 normal human subjects, (5.0 ± 1.0µg/ml). In contrast, our sTfR values were much higher than those obtained in an African population from rural Zimbabwe (N 75, 2.5 ± 0.62µg/ml) (28). The differences in these somewhat similar populations may be due to the fact that Khumalo et al (28), defined normal iron status as SF between 20 300µg/L and TS 15 50%, whereas we used SF 30 200µg/L for females and 30-300µg/L for males with similar TS value.

Measurement of SF is currently the accepted laboratory test for diagnosing iron deficiency, and an SF value of less than 15µg/L is a highly specific indicator of iron deficiency (14). However, because ferritin is an acute phase reactant, it may be inappropriately increased even when subjects are iron deficient. In such cases a bone marrow biopsy or a trial of iron therapy may be required (14) (23). The determination of sTfR is noninvasive and sensitive for evaluating bone marrow iron stores, and provides a good alternative to bone marrow aspirate examination, an invasive procedure that can be inadequate for interpretation in 35% of cases (4) (9) (10). We used SF less than 30µg/L to define iron deficiency because previous reports had shown than this value provides better positive predictive values for IDA (14). The sTfR concentrations of the iron deficient group were significantly higher than those of subjects with normal SF levels, P < 0.001. Though TS is thought to provide little diagnostic value over ferritin, we observed similar sTfR pattern in the iron status categories using either TS or SF, particularly with the normal groups (normal SF or TS 15 50%). Of great significance was the inconsistency of sTfR concentrations when TS together with SF were taken into consideration. In those subjects with SF less than 30µg/L but TS within the normal range (category c, table 3), the sTfR levels were similar to those of subjects classified as normal (category a, table 3) but significantly lower than subjects with both TS and SF reduced, p < 0.0001. However, the sTfR-log ferritin index of these subjects was significantly higher than the normal iron status group, p < 0.0001, but remained significantly lower than that of subjects with reduced SF and TS, p < 0.0001. Based on these results we recommend use of sTfR-log ferritin index in individuals with ambiguous sTfR results.

In Caucasians, TS is the test most often used to screen for hematochromatosis, however in African iron overload, both SF and TS are generally used. In African iron overload, normal TS values in the presence of elevated SF levels have previously been observed (29). In iron loading disorders, the significance of sTfR measurement as a marker of iron status is controversial. In subjects with either hemachromatosis or African iron overload, sTfR concentrations either similar (12) (19) or lower (28) (30) than those of normal human subjects have been reported. Only 4 subjects in our study could be classified as having iron overload based on SF and TS values and the mean sTfR concentrations of these individuals was reduced to normal (3.4 ± 2.0µg/ml). In addition, the sTfR concentrations of the individuals with raised SF but normal TS (category e, table 3) was not significantly different from that of subjects classified as having normal iron status (category b, table 3).

In conclusion, our findings suggest that sTfR ferritin index may be used together with other parameters of iron stores in the diagnosis of iron deficiency, particularly when sTfR concentration results are equivocal. However, we do not recommend the use of sTfR concentrations in the diagnosis of iron overload because of the overlap in the values between subjects with iron overload and those with normal iron stores.

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Conflict of Interest Statement

None declared.

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Table 1: Baseline laboratory parameters of subjects.

	Males (N 76)	Females (N 295)	P
Age (years)	52.2 ± 16.5	47 ± 16	
Age range	19 79	15 - 85	
Serum Fe (µmol/L)	12.6 ± 4.8	11.2 ± 4.0	0.008
Transferrin (g/L)	2.0 ± 0.5	2.2 ± 0.6	0.007
% TS	26.6 ± 11.4	22 ± 9.3	< 0.001
**Ferritin (µg/L)	167 (184, 401)	59 (78, 101)	< 0.001
sTfR(µg/ml)	4.9 ± 2.9	5.7 ± 3.3	0.07
sTfR ferritin index	2.3 ± 1.5	3.6 ± 3.1	0.001
CRP (mg/L)	3.9 ± 4.1	3.9 ± 3.8	0.9
ALT (U/L)	9.7 ± 4.6	8.7 ± 7.1	0.31
Haemoglobin (g/dl)	13.6 ± 1.4	12.8 ± 1.0	0.001
MCH (pg)	29.2 ± 2.0	29.7 ± 2.3	0.5
MCV (fl)	87.1 ± 6.5	89.9 ± 8.4	0.2
Platelet count	308 ± 76	284 ± 63	0.2

P-differences between men and women

** Ferritin; median values (CI)

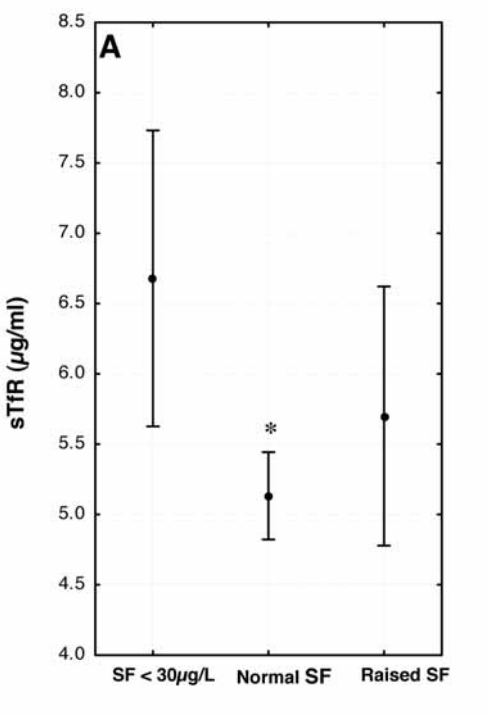
Table II. Spearman's correlation of soluble transferrin receptors and soluble transferrin log ferritin index with indirect measures of iron status.

	sTfR			sTfR ferritin index		
	r^2	r	*P*	r^2	r	*P*
Serum iron	0.08	- 0.3	< 0.0001	0.05	- 0.23	< 0.0001
Ferritin (log)	0.03	- 0.17	< 0.0001			
%TS	0.05	- 0.22	< 0.0001	0.07	- 0.26	< 0.0001
Hb	0.01	- 0.11	0.26	0.02	- 0.16	0.11
MCV	0.02	- 0.13	0.21	0.01	- 0.10	0.37

Table III: sTfR and sTfR ferritin index levels in the 5 breakpoints of serum ferritin and transferrin saturation.

Iron parameters categories	Number	sTfR (µg/ml)	95% CI	P value	sTfR-ferritin index	95% CI	P value
(a)SF < 30µg/L and TS < 15%	31	8.8 ± 6.5	6.4, 11.2		7.6 ± 5.8	5.4, 9.7	
(b) SF normal and TS 15 50%	202	5.0 ± 2.4	4.6, 5.3	< 0.0001	2.6 ± 1.2 **	2.4, 2.7	<0.0001
(c) SF < 30µg/L and TS 15 50 %	51	5.4 ± 2.8	4.6, 6.2	0.0002	4.6 ± 4.1 **	3.5, 5.8	<0.0001
(d) SF normal and TS < 15%	35	6.3 ± 2.6	5.4, 7.2	0.03	3.4 ± 1.4	2.9, 3.9	<0.0001
(e) SF raised and TS 15 50%	37	6.0 ± 3.1	4.9, 7.0	0.008	2.4 ± 1.3 **	1.9, 2.8	<0.0001

P value: differences from category (a), ** sTfR log ferritin index other statistical significant differences between categories: (b) and (c), P < 0.0001; (c) and (e), P 0.003.



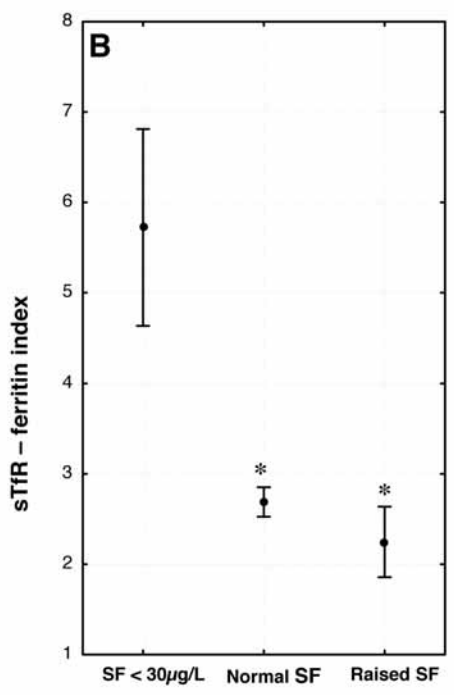
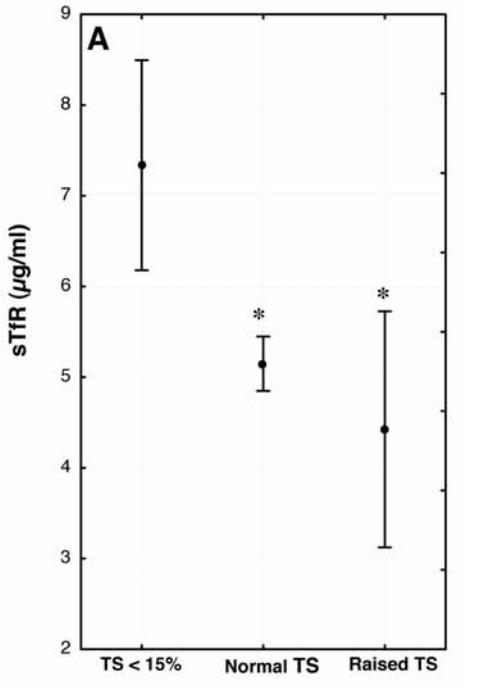


Figure 1.
Plot of means and 95% confidence interval. * significant difference from SF < 30µg/L, P ≤ 0.05. **A**; Soluble transferrin receptor concentrations according to the three breakdown points of ferritin: mean ± SD and (95% confidence interval), SF < 30µg/L (N 83), 6.7 ± 4.8 (5.6, 7.7) µg/ml; normal SF (N 242), 5.1 ± 2.5, (4.8, 5.4) µg/ml and raised ferritin (n 46), 5.7 ± 3.1 (4.8, 6.6) µg/ml. **B**; Soluble transferrin receptor log ferritin index according to the three breakdown points of ferritin: SF < 30µg/L 5.7 ± 5.0(4.6, 6.8); normal SF 2.7 ± 1.3 (2.5, 2.9) and raised SF 2.2 ± 1.3 (1.9, 2.6).



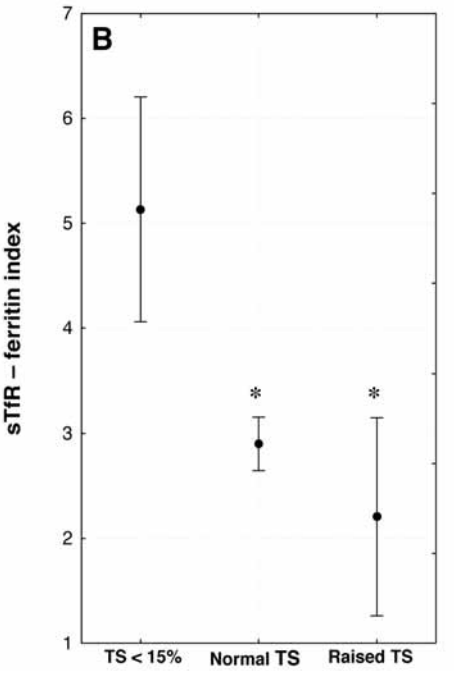


Figure 2.
Plot of means and 95% confidence interval. * significant difference from TS < 15%, P ≤ 0.05. **A**; Soluble transferrin receptor concentrations according to the three breakdown points of transferrin saturation: mean ± SD and (95% confidence interval), TS < 15% (N 71), 7.3 ± 4.8 (6.2, 8.5) µg/ml; normal TS (N 290), 5.1 ± 2.6, (4.8, 5.4) µg/ml and raised ferritin (N 9), 4.4 ± 1.7 (3.1, 5.7) µg/ml. **B**; Soluble transferrin receptor log ferritin index according to the three breakdown points of transferrin saturation: TS < 15% 5.1 ± 4.5(4.1, 6.2); normal TS 2.9 ± 2.2 (2.6, 3.2) and raised TS 2.2 ± 1.3 (1.3, 3.1).