ORIGINAL ARTICLE

Development of A Mathematical Equation to Predict Serum Total Bilirubin Level Correlating Body Mass Index (BMI)

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ABSTRACT

A descriptive, cross-sectional study was conducted to derive a mathematical equation to predict the serum total bilirubin level in terms of body mass index (BMI). We recruited 109 apparently healthy women within 20-28 years. The height and weight were measured using standard protocol to calculate the BMI. The serum total bilirubin level was measured by bilirubin total kit (VOX method) with Mindray BS-240 fully automated biochemistry analyzer. Percentage distribution of individuals according to the BMI categories was 25.7, 28.4, 19.3 and 26.6% for underweight, normal, overweight and obese, respectively with the median BMI of 21.3 kg/m², (interquartile range (IQR) of 6.9 kg/m²). The median serum total bilirubin level was 0.69 mg/dL with the IQR of 0.21 mg/dL. The underweight group had the maximum serum total bilirubin median value (1.12 mg/dL) whereas the obese group had the minimum median value (0.41 mg/dL). The serum total bilirubin level was negatively correlated with BMI ($r=-0.686$, $p<0.001$). Based on the findings, the mathematical model derived was "serum total bilirubin level (mg/dL)=0.1+13.051/BMI". This shows when there is an increase in 1/BMI by one unit, serum total bilirubin level is predicted to be increased by 13.051 units. A statistically significant moderately strong negative relationship was observed between serum total bilirubin levels and BMI in the study population.

Keywords: Mathematical equation, serum total bilirubin, body mass index, underweight, overweight, obese

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INTRODUCTION

Bilirubin is a bile pigment and it is the end product of heme catabolism[1]. The physiological range of serum bilirubin is 5-17 µmol/L. Although the high concentrations of serum bilirubin associates with harmful effects[2], the studies done during past decades have been shown that bilirubin has many important functions in the human body[3]. Health benefits of bilirubin are antioxidant and anti-inflammatory actions, anti-atherogenic and immunomodulatory effects, inhibition of carcinogenesis, contribution to energy homeostasis and involvement in cell signaling pathway[4]. Other than that, it acts as a hormone, an important prognostic marker in cardiovascular diseases[3] and a pre-disease biomarker for developing metabolic syndromes including atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and chronic obstructive pulmonary diseases (COPD)[3,5-7].

"Obesity" is a condition of excess adipose tissue mass and it has been an epidemic in nearly every

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country in the world[8]. Due to the factors such as overconsumption of energy-dense foods like lipids, sedentary life style, effects of genetic and endocrine factors increase the energy storage in adipose tissue and lead to adverse health effects[9]. Body mass index (BMI) is the best parameter to assess the magnitude of the obesity. It has been reported that, bilirubin level is affected by body fat level[10].

The modulation of serum bilirubin is an effective therapy for obesity and obesity-induced pathological conditions[6]. There are several ways to modulate serum bilirubin level as even a tiny amount of elevation of serum bilirubin level leads to clinical benefits. It can be achieved by making lifestyle changes such as non-smoking, avoiding alcohol intake, regular physical activity, and use of herbal products as a part of the diet plan. It helps to manage the BMI in a healthy manner[11].

However, according to the published data related to serum bilirubin and body fat, the findings are less supportive to implement to the Asian countries, especially with reference to the BMI of Asia-Pacific categorization. If there is an association between BMI according to the Asia-Pacific categorization and bilirubin level, a BMI cut-off value can be established to minimize the improvement of diseases in healthy individuals even though they are obese. And also, a mathematical model can be derived to express bilirubin level in terms of BMI. Thereby, BMI could be able to use as a screening tool. Therefore, the aim of this study was to investigate the correlation between the serum total bilirubin level and BMI in a selected population in order to develop a mathematical equation to predict the serum total bilirubin level.

METHODS

This is a descriptive cross-sectional study with laboratory investigations. The study population included 109 healthy women (Sinhala, Buddhist) within age range of 20-28 years. Hyperbilirubinemic patients, individuals with smoking, alcohol consumption, high physical activities, renal failure, liver diseases, cardiac diseases, diabetes mellitus, metabolic syndrome, hypertension and respiratory diseases, individuals undergone surgeries and medication, pregnant and lactating women were excluded from the study.

At first to determine the body mass index (BMI) of each individual, body weight was measured using a weighing scale, which was pre-calibrated with known weights and the weight was recorded in kilogram. The standing height was measured in centimeters using a stadiometer. Then, BMI was calculated using the following formula; BMI=Weight in kilogram/(Height in meter)^2. Then, each individual was included in the appropriate BMI category according to the Asia-Pacific cut-off points (i) BMI <18.5 kg/m^2 (underweight) (ii) BMI between 18.5 to 22.9 kg/m^2 (normal weight) (iii) BMI between 23.0 to 24.9 kg/m^2 (overweight) and (iv) BMI ≥ 25.0 kg/m^2 (obese)[12].

Two milliliter of whole blood was collected from each participant into the plain tube. The collected blood specimens were left undisturbed at room temperature for 30 minutes by keeping the tubes in upright position. After 30 minutes, the tubes were checked for clot formation. Then, the tubes were gently tapped in order to detach the clot from the bottom of the tubes. Next, the tubes were centrifuged at 3000 rpm for 5 minutes and the supernatant was collected. Bilirubin total Kit with VOX method was used to determine the serum total bilirubin level. The serum total bilirubin level was measured using the Mindray BS-240 fully automated biochemistry analyzer.

Data analysis was done using IBM Statistical Package for Social Sciences (SPSS) software version 27.0 for Windows. The normality test (Shapiro-Wilk) was used to see whether the distribution of BMI and serum total bilirubin in the study population was normal or not. The Spearman's correlation coefficient was used to evaluate the correlation between serum total bilirubin level and BMI whereas Kruskal-Wallis test was used to compare the median value of serum total bilirubin level separately across BMI categories. The Mann-Whitney U-Test was performed to compare the statistically significant difference between two BMI categories

RESULTS

The BMI of the study population was ranged from 14.8 to 34.7 Kg/m^2. The individuals had been distributed among four BMI categories as given in the Table 1. The distribution of BMI within the study population is indicated in the Figure 1. The BMI data were deviated significantly from the normal distribution (p=0.004). Due to the non-normal distribution, BMI was expressed as median and interquartile range (IQR). The median value of the BMI was 21.3 Kg/m^2 and the IQR was 6.9 Kg/m^2.

The serum total bilirubin in the study population was ranged from 0.41 to 1.12 mg/dL. These values were significantly deviated from the normal distribution (p=000) and it is indicated in the Figure 2. The median serum total bilirubin level was 0.69 mg/dL and IQR was 0.21mg/dL. The distribution of serum total bilirubin level according to the BMI category is indicated in the Table 2. The BMI had a larger IQR compared to serum total bilirubin, signifying a wider distribution of BMI than serum total bilirubin. Serum total bilirubin level in each BMI category was normally distributed ($p>0.05$). But, variances of serum total bilirubin level in all four BMI categories were not equal ($p<0.05$). According to Kruskal-Wallis test, there was a significant difference in medians of serum total bilirubin level in BMI groups ($p<0.001$). There was a significant difference between median serum total bilirubin levels of underweight and normal weight females ($p<0.001$). The difference between median serum total bilirubin levels of normal weight and overweight individuals was not significant ($p>0.05$) and overweight and obese individuals was marginally significant ($p>0.05$).

The relationship between serum total bilirubin and BMI in the study population is shown in Figure 3. The Spearman's correlation coefficient between BMI and serum total bilirubin level was -0.686. This indicates a negative relationship between these two variables. The -0.686 suggested a statistically significant and moderately strong negative association between BMI and serum total bilirubin level ($p<0.01$).

Table 1: Distribution of study population according to the BMI category

BMI category	Frequency	Percentage
Underweight	28	25.7
Normal	31	28.4
Overweight	21	19.3
Obesity	29	26.6
Total	109	100

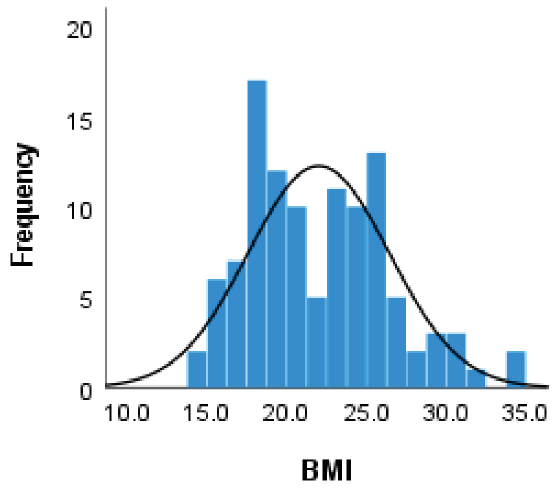

Figure 1: Distribution of BMI in the study population.

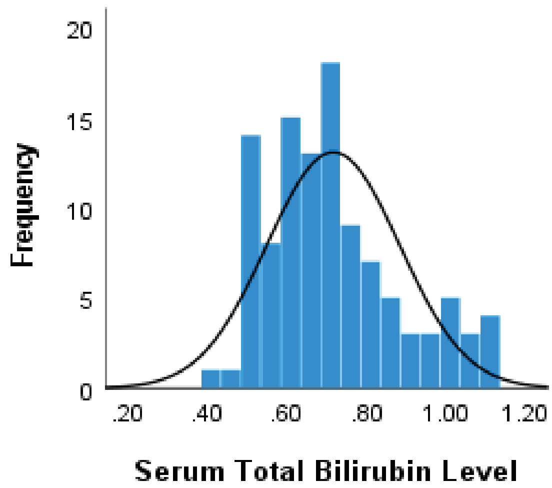

Figure 2: Distribution of serum total bilirubin level in the study population

Table 2: Distribution of serum total bilirubin level in the study population according to BMI category

BMI category		Serum total bilirubin level (mg/dL)
Underweight	Minimum	0.52
	Maximum	1.12
	Median	0.87
	Interquartile range	0.29
Normal	Minimum	0.46
	Maximum	1.04
	Median	0.72
	Interquartile range	0.19

BMI category		Serum total bilirubin level (mg/dL)
Overweight	Minimum	0.49
	Maximum	0.80
	Median	0.64
	Interquartile range	0.13
Obesity	Minimum	0.41
	Maximum	0.74
	Median	0.60
	Interquartile range	0.14

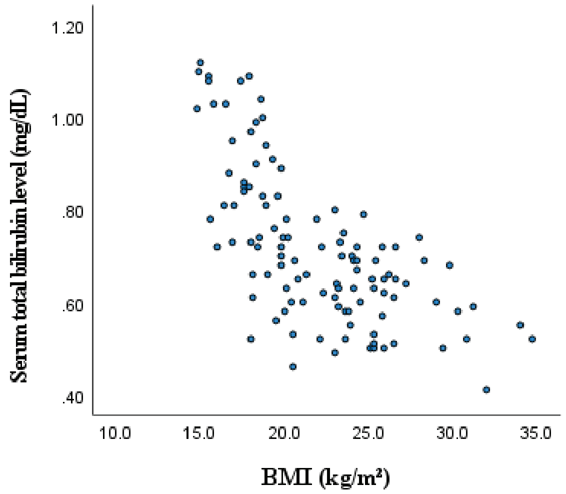

Figure 3: Relationship between serum total bilirubin and BMI in the study population

Four potential models; Linear, Logarithmic, Inverse, and Exponential were tested to derive the mathematical model. The best model which had the highest R^2 (0.524) was in "Inverse model" ($p<0.01$). It concludes that the Inverse model explains 52.4% of total variation of serum total bilirubin with regard to BMI (see Table 3). The p-value <0.01 indicated that the model is statistically significant.

Table 3: Model summary and parameter estimates

Equation	Model summary					Parameter estimates	
	R^2	F	df1	df2	Significant value	Constant	b1
Linear	0.451	87.904	1	107	0.000	1.272	-0.025
Logarithmic	0.493	103.908	1	107	0.000	2.529	-0.590
Inverse	0.524	117.903	1	107	0.000	0.100	13.051
Exponential	0.451	87.747	1	107	0.000	1.479	-0.034

R^2 = Proportion of variance in serum total bilirubin level explained by BMI
F = Statistical significance of the regression model
df1 = Number of independent variables
df2 = Residual degrees of freedom
b1 = Coefficient of serum total bilirubin level

By using the figures related to Inverse model, the following mathematical model was developed:

Total serum bilirubin level (mg/dL) = 0.1+13.051/BMI

This shows that when there is an increase in 1/BMI by one unit, serum total bilirubin level is predicted to be increased by 13.051 units. The standard error (SE) for the constant (0.1) in the Inverse model was 0.058 ($p<0.01$) whereas the SE for the coefficient of 1/BMI (13.051) was 1.202 ($p<0.01$).

DISCUSSION

We obtained a significant inverse relationship between serum total bilirubin and BMI and the Spearman's correlation coefficient between BMI and serum total bilirubin level was -0.686. This negative sign indicates a negative relationship between these two variables.

The study carried out by Bergmann et al showed an inverse correlation between total and direct bilirubin levels and BMI[13] whereas Jenko-Praznikar et al. showed that both direct and indirect serum bilirubin levels were lower in the overweight group compared to normal weight group[14]. In addition to that, Kipp et al. showed that bilirubin level is negatively correlated with adiposity in obese men and women, and its catabolized product, urobilin, is positively associated with insulin resistance[15]. The study conducted by Takei et al. on patients with type 2 diabetes found a substantial negative relationship between serum bilirubin concentration and BMI[16]. Another study conducted by Belo et al. observed a negative and significant correlation between BMI and total bilirubin levels in obese subjects, but not in the non-obese control group[10]. Furthermore, Rodrigues et al. reported a significant inverse correlation between BMI and plasma total bilirubin concentration[17]. The study carried out by Tanaka et al. reported that serum bilirubin level is not related with BMI in men, but women have given a remarkable lower concentration with high BMI (≥27.5kg/m^2)[18]. Our finding is supported by all of the above mentioned studies. In contrast to our finding, Zucker, Horn & Sherman reported that there was no significant relationship between blood bilirubin levels and BMI[19].

In the present study, the inverse association between BMI and bilirubin level can be due to several factors. Firstly, the increased bilirubin concentration may be the result of increased oxidative stress, which is associated with overweight and obesity. Bilirubin, at its physiological concentrations, acts as an effective endogenous antioxidant by scavenging reactive oxygen species, which can contribute to oxidative stress by oxidizing bilirubin into biliverdin. Obesity is also associated with a chronic state of low-grade inflammation that potentially leads to a decrease in bilirubin levels[14]. A previous study reported that obese individuals have lower bilirubin levels than their leaner counterparts and discovered that the uridine diphosphate-glucuronyltransferase1A1 (UGT1A1) enzyme, which is responsible for removing bilirubin from blood circulation, is increased in the liver with obesity, potentially contributing to this negative association[15]. Furthermore, biliverdin reductase-A (BVRA), an enzyme involved in the conversion of biliverdin to bilirubin, has been found to be lower in obese persons with insulin resistance[16].

In the present study, we tried to derive a mathematical model to express serum total bilirubin level in terms of BMI. For that, four potential models were tested; Linear, Logarithmic, Inverse, and Exponential. The best model which had highest R^2 (0.524) was in the Inverse model. The Inverse model explains that 52.4% of the total variation of serum total bilirubin level. The mathematical model is "Total serum bilirubin level (mg/dL) = 0.1+13.051/BMI". This shows when there is an increase in 1/BMI by one unit, serum total bilirubin level is predicted to be increased by 13.051 units. Using this formula, individuals can modulate their serum total bilirubin levels and effectively manage their BMI while decreasing the risk for various diseases such as cardiovascular disease, diabetes mellitus, and metabolic syndrome. This serum bilirubin modulation can be achieved through a combination of strategies, including maintaining a healthy BMI and making lifestyle changes such as non-smoking, avoiding alcohol intake, engaging in regular physical activity, and incorporating herbal products as part of their diet plan[11].

CONCLUSION

There was a statistically significant and moderately strong negative relationship between serum total bilirubin level and BMI in our study population. Higher serum total bilirubin levels were associated with low level of BMI values (underweight) while lower serum total bilirubin levels were associated with high level of BMI values (obesity). The mathematical model derived was "Serum total bilirubin level = 0.1+13.051/BMI".

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Authors' contribution: Concept and design of the study: WGNM Bandara, AMB Priyadarshani; Participants selection and Data collection: WGNM Bandara, ADBR Gunasekara, MG Vidyathilaka; Data compilation and analysis: WGNM Bandara, ADBR Gunasekara, MG Vidyathilaka, P Dias; Manuscript preparation, editing and final submission: WGNM Bandara, ADBR Gunasekara, MG Vidyathilaka, P Dias, AMB Priyadarshani.

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