Effects of age and sex in several biochemical parameters in healthy subject in Jeddah Saudi Arabia

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Abstract: This project study the liver function tests in different age groups and in both males and females individuals. Specimens collected were sera from groups of normal persons 30 males and 30 females and age groups from 2-12, 13-49, and 50-65 years. Parameters measured included bilirubin, direct bilirubin, alanine transaminase (ALT), gamaglutamyl transferase (GGT), blood urea nitrogen (BUN), sodium (Na), potassium (K) and chloride (Cl). The results show significant decrease in bilirubin and direct bilirubin in all groups of females whereas the mean ALT values were higher in men than in women in age 13-49 and 50-65 years. GGT and BUN values were higher in men than in women in age 2-12 and 13-49 yeas. Potassium (K) values were higher in men compared with women in age 2-12 and 50-65 years. Serum concentrations of sodium (Na) and chloride (Cl) did not show sex differences. This study showed that there was evidence for age and sex-related differences in several liver function test parameters.
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Key words: Age, Sex, bilirubin, direct bilirubin, alanine transaminase (ALT), gamaglutamyl transferase (GGT), blood urea nitrogen (BUN), sodium (Na), potassium (K) and chloride (Cl)**.**

1- Introduction

The measurement of the serum activities of enzymes is helpful in the diagnosis and management of liver disease. Moreno et al (1978) showed that there were no significant variations were found concerning the levels of BUN in male students between 9 and 16 years compared with a sample of adult males between 20 and 45 years . Against that, they saw significant age variations for the levels of uric acid. Cheng et al (1979) analyzed uric acid, BUN, ALT, and total bilirubin in healthy children. For each test age- and sex-related variations were assessed and normal values were estimated for six different age groups. Gardner and Scott (1980) analyzed blood specimens from randomly selected adults aged 19-88 years were used to establish age- and sex-related reference ranges for plasma urea and urate. Gómez *et al.* (1984) determined normal reference values and the influence of age and sex on uric acid, Na, K, Cl, total bilirubin and ALT in serum in children (ages one week to 14 years). Rodger *et al* .(1985) used 8 Analyzer to establish normal reference intervals for plasma urea, and electrolytes in healthy adults. All of these analytes showed significant sex-related differences; except chloride showed age-related changes. Nicolau *et al.*(1987) showed significant differences in the circadian rhythms in total serum bilirubin, BUN and GGT in elderly men and women and clinically healthy boys and girls. Lockitch *et al.*(1988) defined age- and sex-specific reference intervals in sera from a healthy population of neonates and children ages one to 19 years. Newborns have higher concentrations of bilirubin than older children. Concentrations of urea, and bilirubin change rapidly postnatally. Outside the neonatal period, no significant age- or sex-related difference was found for serum bilirubin. There was no sex-related difference in reference intervals for urea, whereas alkaline phosphatase values peak later in boys. Burritt *et al.*(1990) determined age- and sex-specific reference intervals variables in serum samples from healthy subjects, 1 to 22 years of age. No significant age or sex differences were found for serum Na, direct bilirubin, K, Cl, and urea showed constant values in children that were higher than adult and lower than adult values in urea. No sex-related differences were seen for these analytes. Creatinine, and uric acid showed an upward trend in values with increasing age. Sex-related differences were noted for these analytes. Khan *et al.*(1997) determined the reference values of serum urea, uric acid, total bilirubin and ALT in healthy population, aged newborn to 80 years. The values in adult females, Cl and elderly subjects were slightly different than adult males. Jagarinec *et al.*(1998) studied the biochemical constituents of sera on school children and adolescents aged 8-18 years compared with a sample of the healthy adult, aged 20-30 years from the same geographical area. Serum K, Na and Cl did not show age or sex differences; total serum bilirubin had

higher reference intervals than the adult . Urea, creatinine, ALT, and GGT, had lower reference intervals than the adult. Work et al .(1999) and Habdous *et al.*(2003) reported that hematological and serum chemistry varied with age and sex. Xiao *et al*.(2004) investigated the differences in serum biochemistry between specific pathogen-free (SPF) and conventional Wistar rats. The serum levels of ALT, BUN, creatinine, and uric acid (UA) were very significantly different between male and female Wistar rats of either conventional or SPF grade, significant differences in ALT, between the female rats of the two grades, the serum levels of ALT and BUN were very significantly different. Lanzarot *et al*.(2005) found sex-dependent differences were observed in gamma-globulins while aspartate aminotransferase increased with age. Ilcol and Aslan (2006) studied indirect reference intervals of the biochemical analyses in healthy subjects of 18-45 years and found that they were comparable, with small differences in lower limits of ALT, creatine kinase, direct bilirubin, sodium, BUN and uric acid (females) and/or upper limits of GGT, ALT, direct bilirubin (males) and uric acid. Levy *et al*. (2006) found that bilirubin and BUN were higher in adults than at birth. Quintó *et al*.(2006) provided reference intervals of hematological and biochemical indices for children aged 1-4. Reference intervals for creatinine show significant differences by age. Gender differences were observed for creatinine values, while for bilirubin there were no significant differences for age or gender. Ichihara *et al*.(2008)observed unacceptably large regional differences in measured values of some analyses even after adjustment for age, sex, and lifestyle variables. Genetic and environmental factors may account for the residual differences. Jekl *et al*.(2011) found that the plasma levels of BUN, ALT and K were significantly lower in adults than in juveniles. Woldemichael *et al*.(2012) reported that biochemical reference ranges currently used in developing countries are derived from data collected from populations living in developed countries. However, it is a fact that there is considerable variation in biochemical reference intervals by several variables. Pineda-Tenor *et al*.(2013) indicated that the reference change values derived from elderly subjects were similar to those published in the young population, both in healthy and diseased individuals.

The aim of the project :

This project study the liver function tests in different age groups and in both males or females individuals.

2- Materials and methods

Specimens collected were sera from group of normal persons 30 males and 30 females from each group and age group from 2-12, 13-49, and 50-65 years. Parameters measured included total bilirubin, direct bilirubin, alanine transaminase (ALT), gamaglutamyl transferase (GGT) , blood urea nitrogen (BUN), sodium (Na), potassium (K) and chloride (Cl). All samples were assayed using the Hitachi 717 analyzer, King Abdulaziz University Hospital.

Statistical analysis:

The statistical evaluations were conducted utilizing conventional Student`s t-test. Comparison of the results was reported at the $p<0.05$ level.

3- Results

The subjects had serum bilirubin, direct bilirubin, alanine transaminase, gamaglutamyl transferase, blood urea nitrogen, sodium, potassium, chloride levels were within normal limits.

The level of total bilirubin in the sera of children age group 2-12 years; male values have a mean=2.45 µmol/L, females values have a mean=1.87 µmol/L, in the age group 13-49 years; males values have a mean= 2.96 µmol/L, females values have a mean=2.11µmol/L, in the age group 50-65 years; male values have a mean= 2.75 µmol/L, females values have a mean=1.99 µmol/L. Most of the values are in the middle of normal range. The level of direct bilirubin in the sera of children age group 2-12 years; male values have a mean= 7.23 µmol/L, female values have a mean=5.10 µmol/L, in the age group 13-49 year; male values have a mean=7.93 µmol/L, female the values have a mean=5.44 µmol/L, in the age group 50-65 years; male values have a mean= 6.87 µmol/L, female values have a mean=6.27 µmol/L. Most of values are in the middle of normal range. The level of alanine transaminase in the sera of children age group 2-12 years; male values have a mean= 13.07 U/L, female values have a mean=14 U/L, in the age group 13-49 years; male values have a mean=25.3 µmol/L, female values have a mean=11.36 U/L, in the group 50-65 years; male values have a mean= 22.4 U/L, female values have a mean=15.27 U/L. Most of values are in the middle of normal range. The level of gamaglutamyl transferase in the sera of children age group 2-12 years; male values have a mean= 15.33 U/L, female values have a mean=11.77 U/L, In the age group 13-49 years; male values have a mean=26.9 U/L, female values have a mean=14 µmol/L, in the age group 50-65 years; male values have a mean= 23.63 U/L, female values have a mean=26.03 µmol/L. Most of values are in the middle of normal range. The level of blood urea nitrogen in

the sera of children age group 2-12 years; male values have a mean= 5.02 mmol/L, female values have a mean=4.10 mmol/L, in the male age group 13-49 years; male values have a mean=5.45 mmol/L, female values have a mean=4.07 mmol/L, in the age group 50-65 years; male values have a mean= 4.84 mmol/L, female values have a mean=5.12 mmol/L. Most of values are in the middle of normal range. The level of Sodium in the sera of children age group 2-12 years; male values have a mean= 141.13 mmol/L, female values have a mean=141.7 mmol/L, In the age group 13-49 years; male values have a mean=140.1 mmol/L, female values have a mean=139.17 mmol/L, in the age group 50-65 years; male values have a mean= 140.7 mmol/L, female values have a mean=141.23 µmol/L. Most of values are in the middle of normal range. The level of Chloride in the sera of children age group 2-12 years; male values have a mean= 101.03 mmol/L, female values have a mean=102.1mmol/L, In the age group 13-49 years; male values have a mean=100.87 mmol/, female values have a mean=102.07 mmol/L, in the age group 50-65 years; male values have a mean= 102.03 mmol/L, female values have a mean=102.83 mmol/L. Most of values are in the middle of normal range for male and female in age group 13-49 and group 50-65 year. The level of Potassium in the sera of children age group 2-12 years, male values have a mean= 4.20 mmol/L, female values have a mean=4.62 mmol/L, in the age group 13-49 years; male values have a mean=4.14 mmol/, female values have a mean=4.31 mmol/L, in the age group 50-65 years, male values have a mean= 4.24 mmol/L, female values have a mean=4.48 mmol/L. Most of values are in the middle of normal range.

Table 1: Some clinical chemistry levels in male and female in various age .

	Male Age Group (years)			Female Age Group (years)		
Parameter	**2-12**	**13-49**	**50-65**	**2-12**	**13-49**	**50-65**
Bilirubin µmol/L	2.45±0.19	2.96±0.25	2.75±0.25	1.87±0.11*	2.11±0.21*	1.99±0.19*
Direct bilirubin µmol/L	7.23±0.35	7.93±0.52	6.87±0.42	5.10±0.18*	5.44±0.47*	6.27±0.41*
Alanine transaminase U/L	13.07±0.82	25.3±1.6	22.4±1.9	14±0.7	11.36±1.13*	15.27±0.98*
Gamaglutamyl transferase U/L	15.33±0.93	26.9±1.19	23.63±1.62	11.77±0.2*	14±1.08*	26.03±1.52
Blood urea nitrogen mmol/L	5.02±0.17	5.45±0.21	4.84±0.17	4.10±0.11*	4.07±0.17*	5.12±0.22
Sodium mmol/L	141.13±0.56	140.1±0.62	140.7±0.68	141.7±0.35	139.17±0.68	141.23±0.69
Chloride mmol/L	101.03±0.64	100.87±0.64	102.03±0.92	102.1±0.37	102.07±0.45	102.83±0.48
Potassium mmol/L	4.20±0.08	4.14±0.11	4.24±0.09	4.62±0.12*	4.31±0.07	4.48±0.08*

Normal range value of total bilirubin in the sera of children age group 2-12 years in male (0.1-4.9 µmol/L), in female (0.7-3.1 µmol/L), in the male age group 13-49 year (0-6 µmol/L), in female (0-4.9 µmol/L), in the male age group 50-65 year (0-6.2 µmol/L), in female (0-4.2 µmol/L). Normal range values direct bilirubin in the sera of children age group 2-12 years in male (1.4-13 µmol/L), in female (1.3-7.1 µmol/L), In the male age group 13-49 years (1.1-14.7 µmol/L), in female (0.3-10.7 µmol/L),In the male age group 50-65 year (1.0-12.6 µmol/L),In female (1.1-11.5 µmol/L). Normal range value of alanine transaminase in the sera of children age group 2-12 year in male (2.6-30.2 U/L), in female (5.7-22.1 U/L), in the male age group 13-49 year (4.1-46.5 U/L), in female (1.6-24.4 U/L), in the male age group 50-65 year (1.7-43.7 U/L), in female (0.7-31.9 U/L). Normal range value of gamaglutamyl transferase in the sera of children age group 2-12 year in male (0.3-31.1 U/L), in female (9-15 U/L), in the male age group 13-49 year (13.8-39.8 U/L), in female (1.6-25.2 U/L), in the male age group 50-65 years (3-43 U/L), in female (8.6-45 U/L). Normal range value of blood urea nitrogen in the sera of children age group 2-12 years in male (2.5-6.0 mmol/L), in female (2.5-6.0 mmol/L), in the male age group 13-49 years (2.86-8.57 mmol/L),In female (2.14-7.5 mmol/L), in the male age group 50-65 year (2.86-8.57 mmol/L), in female (2.14-7.5 mmol/L). Normal range value of Sodium in all age in male and female (135-148 mmol/L). Normal range value of Chloride in the sera of children age group 2-12 years in male and female (102-112 mmol/L), In male and female in age group 13-49 and group 50-65 year (100-108 mmol/L). Normal range value of potassium in the sera of children age group 2-12 years in male and female (3.5-5.8 mmol/L), in male and female in age group 13-49 and group 50-65 year (3.5-5.5 mmol/L).

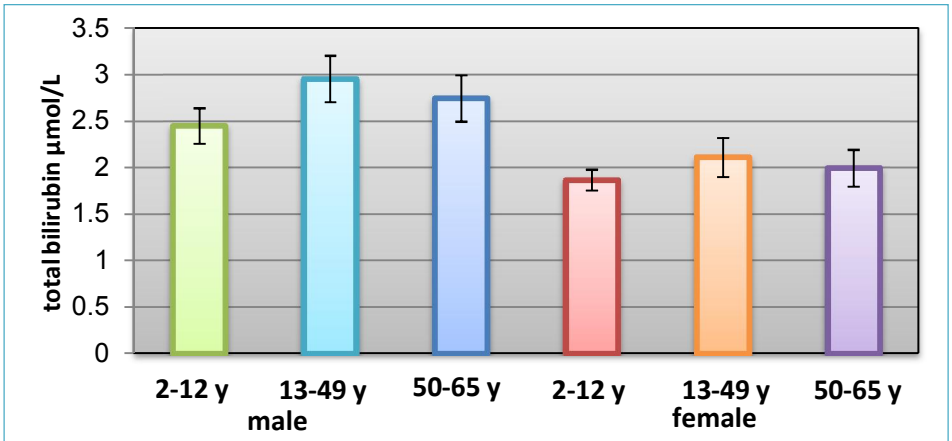

Fig.(1): total bilirubin µmol/L level in various age groups

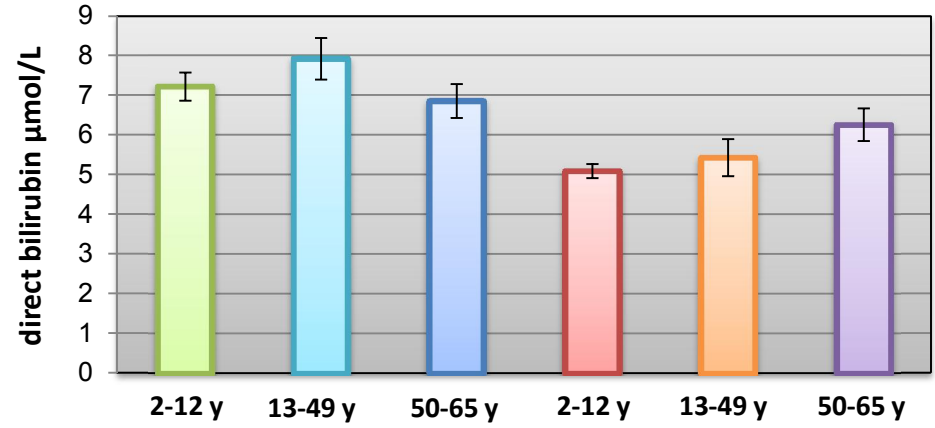

Fig.(2): direct bilirubin µmol/L level in various age groups

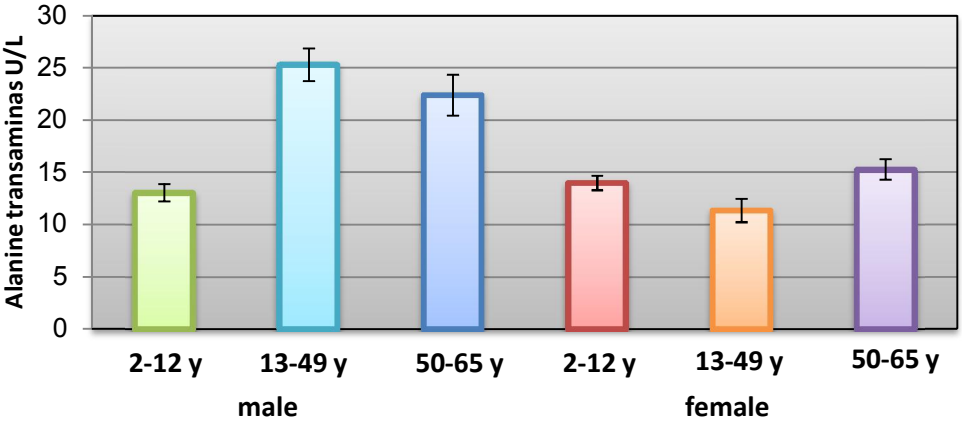

Fig.(3): Alanin transaminase U/L level in various age groups

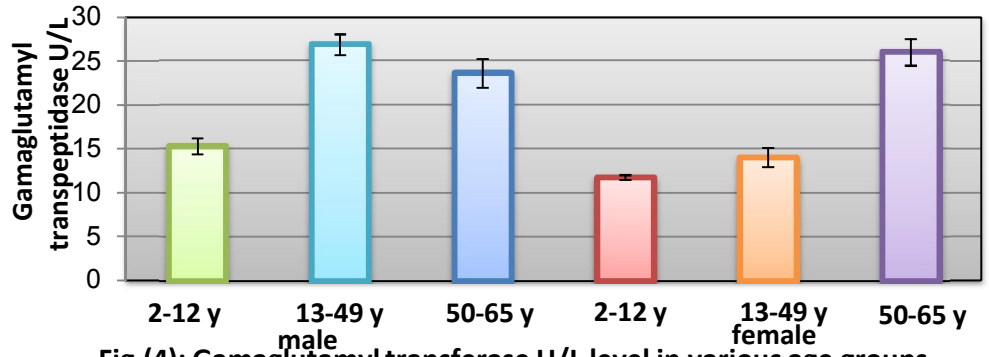

Fig.(4): Gamaglutamyl transferase U/L level in various age groups

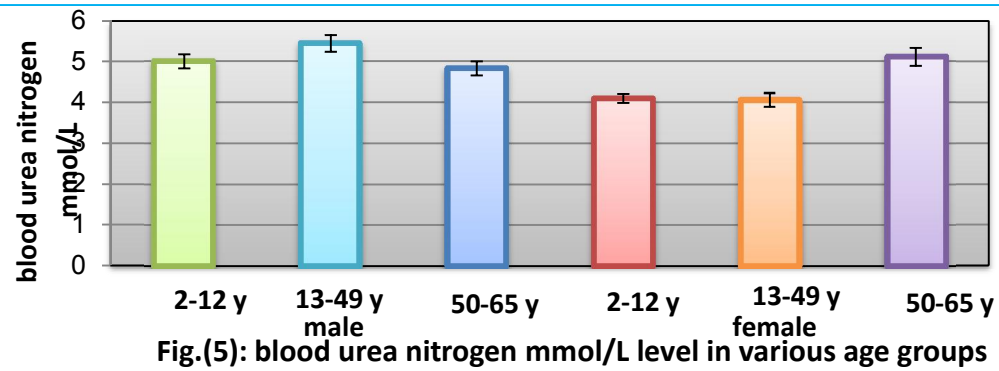

Fig.(5): blood urea nitrogen mmol/L level in various age groups

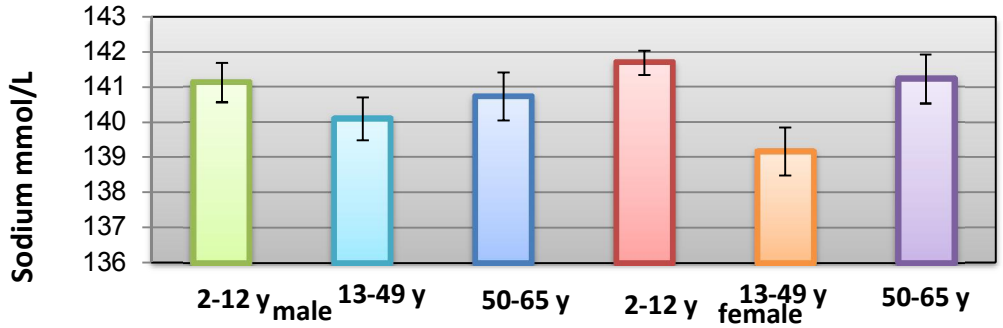

Fig.(6): Sodium mmol/L level in various age groups

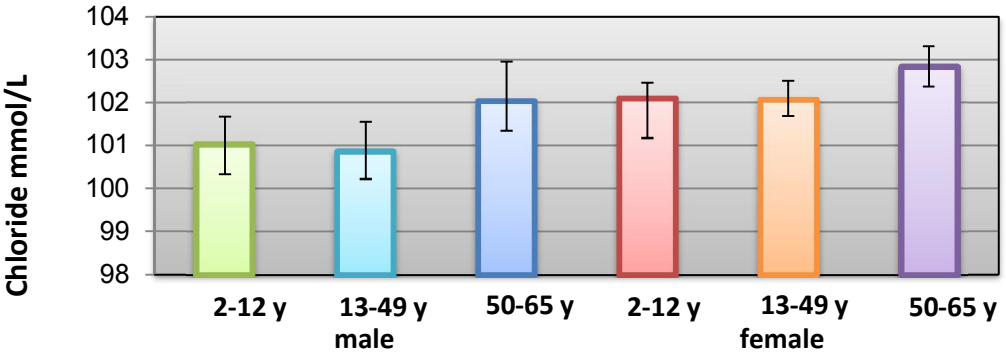

Fig.(7): Chloride mmol/L level in various age groups

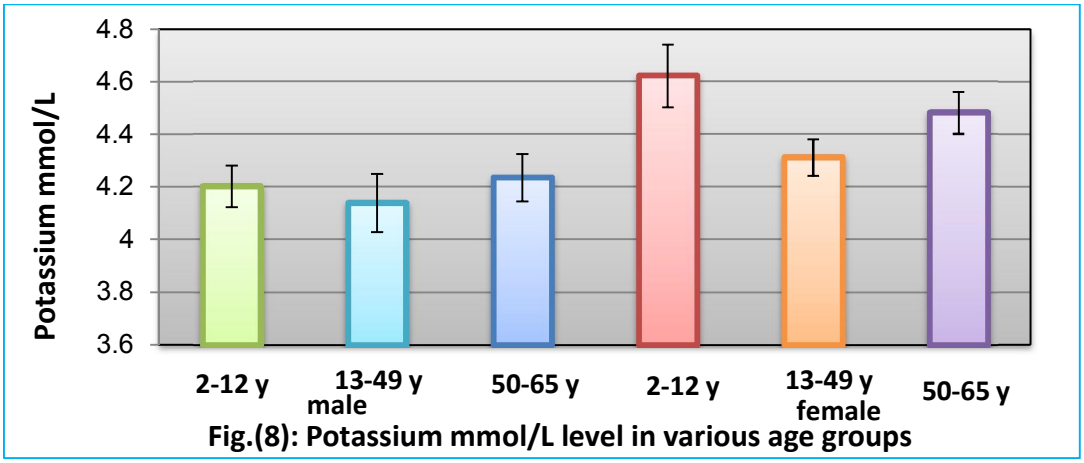

Fig.(8): Potassium mmol/L level in various age groups

4- Discussion

There was evidence for age and sex-related differences in several biochemical parameters. The result show significant decrease in bilirubin and direct bilirubin in all group of females, decrease in alanine transaminase and gamaglutamyl transferase in female in age 13-49 and 50-65 year, also there was significant decrease in blood urea nitrogen in females in age groups 2-12 and 13-49 year

Cherian and Hill .(1978); Work .(1999); Slev *et al.* (2010) and Clifford *et al*.(2011) showed that certain chemical constituents showed statistically significant relationships with age and sex in children and adolescents aged .

The concentrations of bilirubin and direct bilirubin are higher in males than females. This increase in bilirubin and direct bilirubin in males may be due to physiological changes in metabolism or that changes in hemoglobin turnover. This is in agreement with these of Scholtz .(2009) who showed that the bilirubin values were higher in males. Moreno (1978) and Reilly *et al*. (1987) found that the variations concerning the bilirubin levels are associated with the metabolic processes during growth. Kraft and Dürr.(1999) observed Several sex-related differences may be explained by the physiological changes in metabolism in females.

Bilirubin is the major breakdown product of hemoglobin and is excreted by the liver as part of the bile (Gilmore and Garvey, 2009). Increases in bilirubin indicate inefficient lymphatic or liver-gallbladder function (Lumeij, 1994).

Bilirubin is reportedly affected by genetic variations (Bayyari *et al*., 1997 and Bathum *et al*., 2001) and the reports of sex differences in red blood picture (Vo *et al*., 1978) indicate that changes in hemoglobin turnover might be the underlying cause of the difference. This notion is supported by Mercke and Lundh (1976) showing the changes of heme catabolism during the human menstrual cycle.

Alanine aminotransferase is a cytoplasmic enzyme that catalyzes the transamination of α-ketoglutarate and l-alanine, forming glutamate and pyruvate (Krat and Dürr, 1999). The activity of ALT is the most popular parameter in hepatology Morańska *et al* . (2004) increase in ALT indicates injury to hepatocytes Bilal *et al*.(2011). In this study we found that the mean of ALT values being higher in men than in women in age 13-49 and 50-65 years. GGT values show higher values in men than in women in age 2-12 and 13-49 year . That may be due to age, gender, body mass index or predictive for metabolic syndrome or future vascular risk or diabetes in healthy individuals who have within-normal-limits concentrations of liver enzymes. This is in agreement with these of Leclercq *et al*.(1999); Morańska *et al* . (2004) ;Shlomai *et al*.(2010); Bilal *et al*.(2011); Chen *et al*.(2014) reported that ALT are significantly higher in men than in women. They suggested that the normal range for ALT value should be adjusted for age, gender and body mass index.

Tenenbaum *et al*. (2003); Lee *et al*.(2006); Oh *et al*.(2006); Liu *et al*.(2007); Chen *et al*.(2008); Goessling *et al*.(2008); Tzima *et al*.(2009); Aigner *et al*.(2010); Steinvil *et al*. (2010) and Ji *et al* .*(*2012) found a strong relationship between increased GGT and ALT levels within the normal range and metabolic syndrome in healthy adults and nonalcoholic fatty liver disease.

Tenenbaum *et al*.(2003); Turgut *et al*. (2006) and Chen *et al*.(2014) showed that the normal concentrations of liver enzymes (GGT and ALT) may directly take part in atherogenesis and evolve as a potential biochemical risk indicator of cardiovascular morbidity and mortality and thus have an application in primary and secondary prevention of cardiovascular disease.

Also, Goessling *et al*.(2008) and Fraser *et al*.(2009) demonstrated a clear association between

elevated ALT and GGT levels within the normal range and diabetes mellitus over 20 years of follow-up. GGT may be a better diabetes predictor than ALT.

Bathum *et al*. (2001) reported that in an elderly group, the ALT and GGT showed high heritability .

The result found that the mean of BUN values being higher in men compared with women in age 2-12 and 13-49 year . That may be due to the gender and age. Gender has stronger effect on BUN, women had relatively lower functional capabilities compared with men. Female sex hormones had some effect on renal function tests. Differences in BUN concentration may reflect dietary differences. That was in line with other reports Kaspar and Norris (1977); Burritt *et al*.(1990); Jagarinec *et al*.(1998); Lai *et al*. (2009) and Woldemichael *et al*.(2012). Male subjects had significant higher concentrations of BUN levels than female subjects.

Aono *et al* .(1994); Nakamura and Miyao .(2008); Sako *et al*. (2011) and Li *et al*. (2012) concluded that the normal range of BUN levels differed between young and elderly subjects, they found that gender and age have stronger effect on BUN. They suggested that women had relatively lower functional capabilities compared with men. Yoshida (1994) suggested that female sex hormones had some effect on renal function tests. Bathum *et al*. (2001) and Inoue *et al*.(2012) suggested that differences in BUN concentration may reflect dietary differences. Aono *et al* .(1994) found that the decline in renal function correlated with age after the seventh decade.

The data indicate that serum concentrations of sodium and chloride did not observe sex differences. Bathum *et al*. (2001) observed that Na and Cl concentration are less dependent on genetic factors because their concentrations are under tight physiological control by homeostatic mechanisms. Whereas potassium being higher in men compared with women in age 2-12 and 50-65 year.

The increase in potassium may be due to increase skeletal muscle and the bone or increased likelihood of osteoporosis in postmenopausal women. Differences in potassium concentrations appear to be determined by the balance between oral intake and excretion in urine and sweat. This is in line with other reports Pierson *et al*.(1974) the lowest potassium values were found to skeletal muscle is attached to bone, and therefore provides support for bone, a loss in skeletal muscle may increase the risk of bone fracture associated with a significantly increased likelihood of osteoporosis in postmenopausal women .

Reidenberg *et al*.(1993) and Sriboonlue *et al*. (1998) reported that differences in potassium concentrations appear to be determined by the balance between oral intake and excretion in urine and sweat .Therefore, variation in dietary intake is likely a more important determinant than differences in potassium excretion. Rodriguez *et al*.(2011) suggested that foods that are low in sodium and high in potassium may contribute to lower left ventricular mass .

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