

# Association of Coffee Consumption with Serum Activities of Liver Enzymes in Normal Saudi Male Population

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**Abstract:** ***Objective:** To examine the association of coffee consumption with serum activities of liver enzymes in Saudi men living in Western region of Saudi Arabia (Makkah) in order to consider the interactive association with major demographic factors. **Materials and Methods:** In this free-living population study blood samples were collected from 200 male subjects ages ranged between 18 and 65 years, with a mean age of  $41.4 \pm 12.69$  years, fasting for 10-12 hours before sample collection. Liver function tests were investigated. **Results:** Heavy coffee drinking was significantly associated with lower levels of serum total cholesterol, total protein, albumin, and AST, but did not affect ALT, and TB. GGT level was not independently associated with coffee consumption. **Conclusion:** The results of the present study demonstrated that heavy daily coffee drinking significantly affects serum cholesterol and protein levels. However, the correlations between coffee consumption habits and these levels require further investigation through epidemiological studies with a larger sample size, including different age groups and populations.*

**Keywords:** Coffee, liver Function Tests, Saudi Arabia

## 1. Introduction

Liver function tests (LFTs) are useful tools in clinical practice to assess potential liver diseases, to monitor treatment responses, and to predict prognosis of the patients with liver diseases. As a battery, LFTs consists most commonly of serum total cholesterol (TC), total protein, albumin, alkaline phosphatase (ALP), total bilirubin (TB), aspartate amino transferase (AST), alanine aminotransferase (ALT), and  $\gamma$ -glutamyl transferase (GGT). However, the interpretation of LFTs should be comprehensive and careful because LFTs can be influenced by many personal and environmental factors, including age, gender [1], body mass index (BMI) [2], alcohol drinking [3] cigarette smoking, Coffee, malnutrition, presence of extra hepatic diseases such as cardiac, musculoskeletal, or endocrine, and status of liver health in itself [4]

In addition, gamma glutamyl transferase ( $\gamma$ GT) is a commonly measured sensitive marker of cholestasis. Indeed, there is evidence in the literature that diet can have an effect upon hepatic enzymes both in animals and in healthy humans [5, 6]

A potentially hepatoprotective effect of coffee has been of interest in the past decades. Coffee consumption has been inversely related to serum levels of gamma-glutamyl transferase (GGT) in different populations [7, 8, 9, 10] and inverse associations with coffee consumption have also been observed for serum activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in several studies [11, 12, 13, 14]. Furthermore, coffee intake has been shown to be related to decreased risks of liver cirrhosis [15] and cancer [16, 17].

Although the influence of alcohol drinking on the liver function has been extensively studied, studies on the effects of coffee drinking or cigarette smoking have been relatively limited. Few studies have addressed on the association between coffee and liver enzymes. Only one study examined the relation between coffee and liver enzymes in women separately, reporting a weaker inverse association for GGT and no association for ALT and AST [18].

According to the international coffee organization, people drink approximately 2.25 billion cups of coffee everyday across the globe. Considering the large amounts of consumed coffee globally and its life time consumption in most individuals, the effects of coffee on health merits great attention. Interestingly, coffee has been suggested to have a potential favorable impact on liver diseases. In North America and Europe, studies have shown that coffee drinking reduces the risk of liver cirrhosis and hepatocellular carcinoma (HCC) [19, 20]

In addition, the protective effect of coffee drinking on the development of HCC has been reported in the Japanese [21].

Moreover, coffee consumption was inversely related with serum levels of ALT and GGT among LFT, especially in heavy alcohol drinkers [22].

The immuno-stimulatory effects of alcoholic extract of the coffee seed on cellular immune function and cyclophosphamide-induced immuno-suppression (CP) in mice have been reported recently [23]. More recently meta-analysis to assess the association between caffeine consumption and prevalence or hepatic fibrosis of non alcoholic fatty liver disease (NAFLD) in observational studies have demonstrated that although total caffeine intake is not associated with the prevalence or hepatic fibrosis of

nonalcoholic fatty liver disease (NAFLD), regular coffee consumption may significantly reduce hepatic fibrosis in patients with NAFLD [24].

Nevertheless, most previous studies deal with the effects of alcohol, coffee, or smoking on one or a few components of LFTs, and there has been a lack of data on the separate effect of coffee drinking on the commonly used all components of LFTs. Moreover, those studies have been reported primarily from Western countries while the study of the effects of these behaviors on LFTs for persons living in Asian countries have had limited study.

In Saudi Arabia, the Arabian coffee “Gahwa”, is a common hot drink. It is a mainstay drink served to guests, consumed almost daily in most Saudi homes, and is served heavily in all local social occasions and gatherings.

Coffee and chocolate sales have trebled in the Arab world in the past decade, with consumption having increased by 100% in Saudi Arabia alone in the past three years. According to economist Hajar Al-Fadl, Saudis now spend more than five billion riyals on coffee each year. The Kingdom of Saudi Arabia has achieved a huge growth in coffee sales with 25% annual growth each year from 2011 to 2014, making it the fastest-growing coffee market in the world [25].

We examined the association of coffee consumption with serum activities of liver enzymes in a free-living population of middle-aged and elderly Saudi men in order to consider the interactive association with major demographic factors.

## 2. Materials and Methods

This study was done after getting approval by the ethics committee of the affiliated institution. All reference individuals enrolled in this study written informed consent prior to the study. Each candidate was required to complete a physical examination by a certified physician to check the health conditions. The exclusion criteria were as followings: presence of acute and chronic infections, digestive diseases, kidney disease, metabolic and nutritional diseases, rheumatic diseases, endocrine disease, circulation system diseases, burns and muscle trauma, hypertension (systolic pressure  $\geq 140$  mmHg and/or diastolic pressure  $\geq 90$  mmHg), excessive smoking (smoking  $> 20$  cigarettes/day), massive blood loss, malnutrition (lose weight, poverty, or special dietary habits) and symptoms (low BMI or significant weight loss), surgery undergone within six months, medication taken within two weeks, blood donation or blood transfusion within four months, strenuous exercise or heavy manual labor. Individuals were further excluded in accordance with one of the following criteria: Positive results for Hepatitis B surface antigen, Hepatitis C antibodies, or HIV antibodies. Two-days food records were compiled by dieticians and the daily intake of energy, carbohydrate, total fat, fat fractions, cholesterol, total protein and dietary fiber were evaluated. The status and quantity of coffee consumption and the duration of coffee consumption (years) by coffee drinkers in the preceding one-year period were determined. Numerous factors, including coffee density/volume (dark, medium and clear), temperature,

coffee consumption type (plain, milk or liquid/powder coffee cream and added sweeteners), factors affecting coffee consumption (season, working conditions and stress) and variations in consumption habits in response to these factors, were taken into consideration.

About three to five milliliters of blood was drawn from the subject population consisted of 200 male subjects who were inhabitants of Makkah, Saudi Arabia. Subject ages ranged between 18 and 65 years, with a mean age of  $41.4 \pm 12.69$  years, fasting for 10-12 hours before sample collection from the antecubital vein by means of vacutainers in the plain tube (no anticoagulant).

Liver function tests (LFTs) including serum total cholesterol (TC), total protein, albumin, total bilirubin (TB), aspartate amino transferase (AST), alanine aminotransferase (ALT), and  $\gamma$ -glutamyl transferase (GGT) were tested. The LFTs were recorded by univariable analyses but serum GGT level was transformed to a natural logarithmic scale to normalize its non-standard distribution.

Samples were allowed to clot for half an hour at room temperature, then centrifuged using ALC centrifuge PK130 made in the U.S.A adjusted at 3400 r.p.m. for five minutes. Serum was transferred into sterile serum container for testing.

Some of the samples tested were excluded from analysis as they showed abnormal look such as visible hemolysis. Collected data was analyzed by Student *t* tests using SPSS program 17.0 (SPSS Institute, Inc.; Chicago, IL, USA) software for statistical analysis. Results were presented as mean  $\pm$  standard deviation. A *P*-value of  $< 0.05$  was considered statistically significant on all analysis.

## 3. Results

Serum total cholesterol levels obtained by mild coffee drinkers ( $< 5$  cup / day-Group-1), moderate coffee drinkers (3-5 cups / day-Group-2) and heavy coffee drinkers (more than 10 cups / day- Group-3) in this study as shown in figure (1) indicated a significant decrease in heavy coffee drinkers when compared with mild and moderate coffee drinkers and their respective non coffee drinker control subjects ( $p < 0.05$ ).

The data for the estimated values of serum total protein, albumin and aspartate amino transferase (AST) levels among the test groups by univariable analyses is shown in (Figures 2,3,4) respectively.

As shown in Figure 2, among mild, moderate and heavy coffee drinkers, the values of total protein were found to be  $7.8 \pm 0.36$ ,  $7.65 \pm 0.35$ , and  $6.50 \pm 0.30$ , gm / dL respectively when compared with their non coffee drinker samples ( $7.9 \pm 0.38$ ) being significantly low in heavy drinker group ( $p < 0.05$ ).

Similarly serum total albumin was found to be significantly decreased ( $p < 0.05$ ) where as decrease in the values of serum AST were found to be highly significant ( $p < 0.005$ ) in heavy coffee drinkers as compared to mild / moderate groups and their respective non drinker control group. This difference

showed about 45% and 63% decrease respectively. (Figures 3 and 4). However a non significant difference was observed in the values of alanine aminotransferase (ALT) and total bilirubin among all kind of coffee drinkers when compared with their respective controls. Serum  $\gamma$ -glutamyl transferase (GGT) level on natural logarithmic scale showed the similar results (Table 1).

#### 4. Discussion

Liver function tests, including assays for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP),  $\gamma$ -glutamyltransferase (GGT), total protein, albumin, and total bilirubin, are generally used to assess hepato-cellular injury, cholestasis, infiltrative disease, biliary obstruction, or synthetic function of the liver. Normally, liver function tests are also used to screen asymptomatic patients/individuals, mostly during regular health check-ups, blood donation, and hospitalization for non-liver related diseases [26]. Appropriate reference intervals of those tests are the most important elements for health evaluation, disease diagnosis, therapy monitoring, and prognosis assessment.

In the present study, LFTs were investigated using univariable analyses. Heavy coffee drinking was significantly associated with lower levels of total cholesterol, total protein, albumin, and AST, but did not affect ALT, GGT and TB.

As our best knowledge, this is the first study in Saudi male population that demonstrated independent effects of coffee drinking on the comprehensive LFTs commonly used in humans. Several previous studies included only limited test items in LFT and their associations with coffee drinking but not with all of these common lifestyle habits were reported. We demonstrated that total cholesterol; total protein, albumin and AST levels were decreased by heavy coffee drinking. Although most previous studies had not mentioned total protein or albumin levels, a study documented that current or past coffee consumption and smoking lower serum albumin, globulin, and all other protein fractions [27]. Moreover, in the chronic hepatitis patients, current smokers were more likely to have lower albumin levels than non smokers [28]. However, the biological mechanisms leading to decreased levels of serum protein and albumin by coffee drinking and smoking have not been studied yet.

Previous epidemiological studies suggested a hepatoprotective effect of coffee drinking on liver function [29]. Furthermore, the protective effects of coffee consumption on AST and ALT have been reported especially in heavy alcohol drinkers [18]. In contrast, several prospective experimental studies demonstrated rather elevated AST and ALT levels after administration of coffee or its ingredient (cafestol) in human subjects, as well as in animal studies [30]

There are numerous limitations when interpreting the studies regarding the health benefits of coffee. Many of the larger studies did not necessarily account for differences in socioeconomic status or other dietary factors [31]. Although one would argue that perhaps patients who had greater

coffee intake were likely healthier, it is found that coffee drinkers tended to have poorer overall health ( $P = 0.29$ ) and vitality scores ( $P = 0.018$ ) compared to non-coffee drinkers [31, 32]. In addition, participants who drank coffee may have had higher cigarette use and alcohol consumption. Also, many studies collected data on coffee intake at only one time point, thus, the coffee intake noted may not have accurately reflected participants intake over time [33]. If it is assumed that caffeine is indeed responsible for the hepatoprotective effects of coffee, then another potential limitation is the variation of caffeine content of coffee within and among coffee shops [34].

Furthermore, many studies failed to define coffee cup size. Although it is clear that coffee intake has hepatoprotective effects, the lack of standardization of coffee cup size amongst various studies leads to ambiguity regarding how much coffee intake is necessary for these effects [35]. Although GGT is a sensitive indicator of liver disease, its specificity is not high enough, since numerous environmental factors and drugs can elevate GGT. Coffee has been implicated to reduce GGT concentration because its anti-oxidant ingredients may preserve intracellular homeostasis, which need GGT [19]. However, in our study, GGT level was not independently associated with coffee consumption.

An additional strength was that we presented independent effects of coffee consumption on the most commonly used comprehensive items of LFTs, adjusted by extensive confounding factors that included age, gender, BMI, and regular medications. Nevertheless, the lack of evidence of the causal-relationship between lifestyle and LFT changes remained a limitation of our study due to its cross-sectional design.

Numerous epidemiological studies suggest that consumption of approximately 3 or more cups of coffee daily will reduce the risk for and severity of hepatotoxicity due to a variety of underlying pathologic processes. While the aforementioned studies provide compelling evidence to suggest that coffee is useful as an alternative medicine in the treatment of the most common types of liver disease, blinded randomized controlled trials must be performed to provide evidence for causation, and to eliminate confounding variables and various types of bias inherent in cross-sectional, cohort, and case-control studies. Additional animal and cell culture studies are also warranted to further elucidate the biochemical basis for the potential beneficial effects of coffee in Saudi male population.

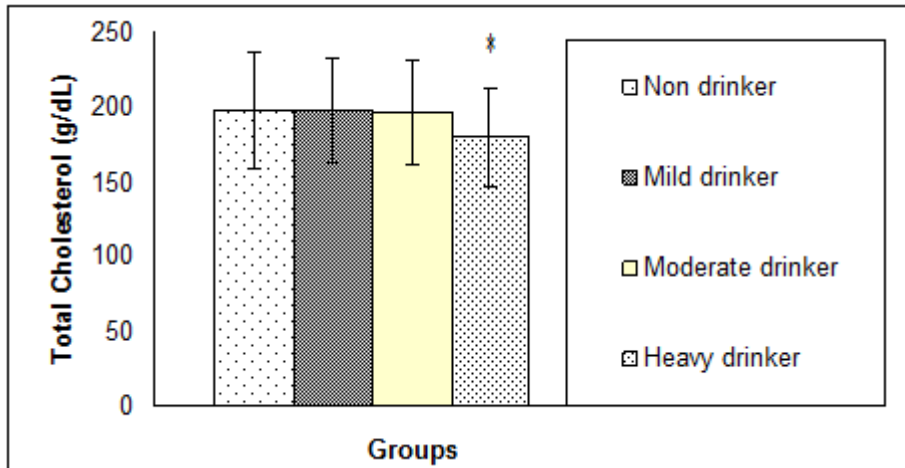
#### References

- [1] Rahmioglu N, Andrew T, Cherkas L, Surdulescu G, Swaminathan R, Spector T, Ahmadi K. "Epidemiology and genetic epidemiology of the liver function test proteins". PLoS One, vol. 4, pp. 4435, 2009.
- [2] Adams L, Knuiman M, Divitini M, Olynyk J. "Body mass index is a stronger predictor of alanine aminotransaminase levels than alcohol consumption". J Gastroenterol Hepatol, vol. 23, pp. 1089-1093, 2008.



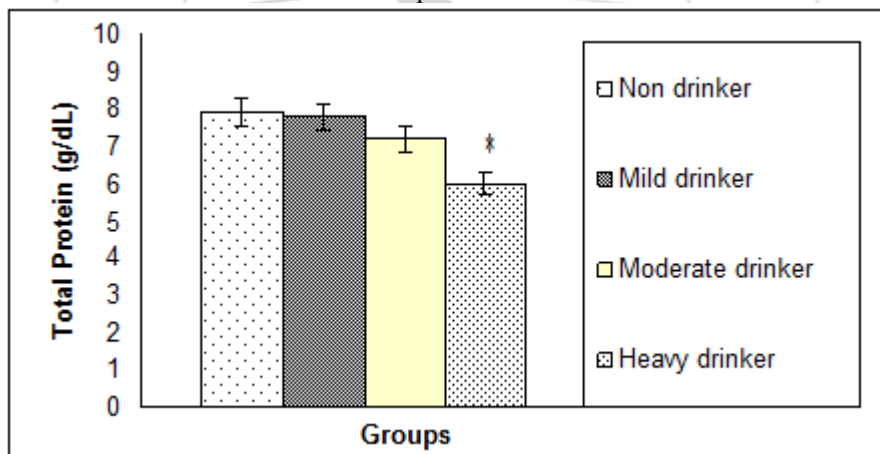
- [3] Sharpe P. "Biochemical detection and monitoring of alcohol abuse and abstinence". *Ann Clin Biochem.* vol. 38, pp. 652-664, 2001.
- [4] Nathwani R, Pais S, Reynolds T, Kaplowitz N. "Serum alanine aminotransferase in skeletal muscle diseases". *Hepatology.* vol. 41, pp. 380-382, 2005.
- [5] Bidlack W, Brown R, Mohan C. "Nutritional parameters that alter hepatic drug metabolism, conjugation and toxicity". *Fed Proc.* vol 45, pp. 142-148, 1986.
- [6] Dannenberg AJ, Yang EK. "Effect of dietary lipids on levels of UDP glucuronosyl transferase in liver". *Biochem Pharmacol.* vol 44, pp. 335-340, 1992.
- [7] Casiglia E, Spolaore P, Ginocchio G, Ambrosio GB. "Unexpected effects of coffee consumption on liver enzymes". *Eur J Epidemiol.* vol. 9, pp. 293-297, 1993.
- [8] Aubin HJ, Laureaux C, Zerah F, Tilikete S, Vernier F, Vallat B, Barrucand D. "Joint influence of alcohol, tobacco, and coffee on biological markers of heavy drinking in alcoholics". *Biol Psychiatry.* vol 44, pp. 638-643, 1998.
- [9] Kono S, Shinchi K, Imanishi K, Todoroki I, Hatsuse K. "Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan". *Am J Epidemiol.* vol. 139, pp. 723-727, 1994.
- [10] Nakanishi N, Nakamura K, Nakajima K, Suzuki K, Tataru K. "Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men". *Eur J Epidemiol.* vol.16, pp. 419-423, 2000.
- [11] Ruhl CE, Everhart JE. "Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States". *Gastroenterology.* vol. 128, pp. 24-32, 2005.
- [12] Klatsky AL, Morton C, Udaltsova N, Friedman GD. "Coffee, cirrhosis, and transaminase enzymes". *Arch Intern Med.* vol. 166, pp. 1190-1195, 2006.
- [13] Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, Umeda T, Wakabayashi K, Imanishi K, Nishikawa H, Ogawa S, Katsurada M, Nakagawa K, Yoshizawa N. "Coffee consumption and serum aminotransferases in middle-aged Japanese men". *J Clin Epidemiol.* vol. 54, pp. 823-829, 2001.
- [14] Masterton GS, Hayes PC. "Coffee and the liver: a potential treatment for liver disease? *Eur J Gastroenterol Hepatol.* vol. 11, pp. 277-283, 2010.
- [15] Tverdal A, Skurtveit S. "Coffee intake and mortality from liver cirrhosis". *Ann Epidemiol.* vol. 13, pp. 419-423, 2003.
- [16] Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S, La Vecchia C. "Coffee drinking and hepatocellular carcinoma risk: a meta-analysis". *Hepatology.* vol. 46, pp. 430-435, 2007.
- [17] Larsson SC, Wolk A. "Coffee consumption and risk of liver cancer: a meta-analysis". *Gastroenterology.* vol. 132, pp. 1740-1745, 2007.
- [18] Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, Zakouji H. "Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers". *Int J Epidemiol.* vol. 27, pp. 438-443, 1998.
- [19] Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S, La Vecchia C. "Coffee drinking and hepatocellular carcinoma risk: a meta-analysis". *Hepatology.* vol. 46, pp. 430-435, 2007.
- [20] Bravi F, Bosetti C, Tavani A, La Vecchia C. "Coffee drinking and hepatocellular carcinoma: an update". *Hepatology.* vol. 50, pp. 1317-1318, 2009.
- [21] Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S. et al. "Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan". *Cancer Sci.* vol. 98, pp. 214-218, 2007.
- [22] Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, Zakouji H. "Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers". *Int J Epidemiol.* vol. 27, pp. 438-443, 1998.
- [23] Mohammad R, Shahid H, Azhar R. "Coffea arabica Seed Extract Stimulate the Cellular Immune Function and Cyclophosphamide-induced Immunosuppression in Mice". *Iran J Pharm Res.* vol. 12 (1). pp. 101-108, 2013.
- [24] Huafeng S, Andrea C. Rodriguez, Ashok S, Seth L, Ghulamullah S, Ambuj K, and Paul M. "Association between caffeine consumption and nonalcoholic fatty liver disease: a systemic review and meta-analysis". *Therap Adv Gastroenterol.* vol 9 (1). pp. 113-120, 2016.
- [25] Al-Fadl H. "2nd International Coffee and Chocolate Exhibition, Riyadh International Convention and Exhibition Center" 26-28 November, 2015.
- [26] Green M, Flamm S. "Technical review on the evaluation of liver chemistry tests". *Gastroenterology.* vol. 123. pp. 1367-1384, 2002.
- [27] Wingerd J, Sponzilli EE. "Concentrations of serum protein fractions in white women: effects of age, weight, smoking, tonsillectomy, and other factors". *Clin Chem.* vol.23 pp. 1310-1317, 1977.
- [28] Nagao Y, Sata M. "Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan". *Virology.* vol. 7. pp 375, 2010.
- [29] Ikeda M, Maki T, Yin G, Kawate H, Adachi M, Ohnaka K, Takayanagi R, Kono S. "Relation of coffee consumption and serum liver enzymes in Japanese men and women with reference to effect modification of alcohol use and body mass index". *Scand J Clin Lab Invest.* vol. 70. pp. 171-179, 2010.
- [30] Urgert R, Essed N, van der Weg G, Kosmeijer-Schuil TG, Katan MB. "Separate effects of the coffee diterpenes cafestol and kahweol on serum lipids and liver aminotransferases". *Am J Clin Nutr.* vol. 65. pp. 519-524, 1997.
- [31] Freedman ND, Park Y, Abnet CC, et al. "Association of coffee drinking with total and cause-specific mortality". *N Engl J Med.* Vol. 366. pp. 1891-904, 2012.
- [32] Modi AA, Feld JJ, Park Y, et al. "Increased caffeine consumption is associated with reduced hepatic fibrosis". *J Hepatol.* vol. 51. pp. 201-209, 2010.

- [33] Gallus S, Tavani A, Negri E, La Vecchia C. "Does coffee protect against liver cirrhosis"? *Ann Epidemiol.* Vol. 12 pp. 202–205. 2002.
- [34] Cadden SH, Partovi N, Yoshida EM. "Possible beneficial effects of coffee on liver disease and function". *Aliment Pharmacol Ther.* vol. 26. pp. 116. 2007.
- [35] Shen H, Rodriguez AC, Shiani A, Lipka S, Shahzad G, Shahzad , Kumar A, Mustacchia P. "Association between caffeine consumption and nonalcoholic fatty liver disease: a systemic review and meta-analysis". *Therap Adv Gastroenterol .* vol. 9. pp. 113-120. 2016.



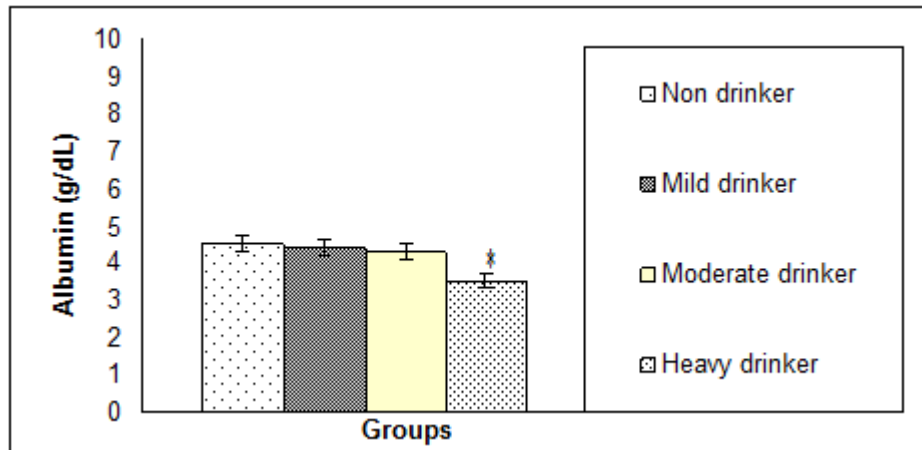
**Figure 1:** Effect of coffee (cups/day) on liver function test (Total Cholesterol) in Saudi normal male subjects. Values are Mean  $\pm$  SD, (n = 200).

*Note:* n = Total number of subjects examined. Coffee drinker values are compared with non drinker control subjects  
 \*p<0.05



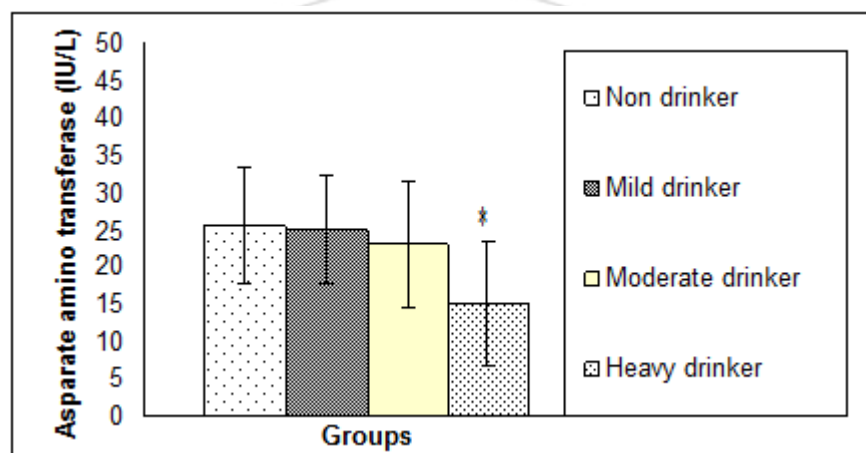
**Figure 2:** Effect of coffee (cups/day) on liver function test (Total Protein) in Saudi normal male subjects. Values are Mean  $\pm$  SD (n = 200).

*Note:* n = Total number of subjects examined. Coffee drinker values are compared with non drinker control subjects  
 \*p<0.05.



**Figure 3:** Effect of coffee (cups/day) on liver function test (Total Albumin) in Saudi normal male subjects. Values are Mean  $\pm$  SD (n = 200).

**Note:** n = Total number of subjects examined. Coffee drinker values are compared with non drinker control subjects  
 \*p<0.05.



**Figure 4:** Effect of coffee (cups/day) on liver function test (Aspartate amino transferase) in Saudi normal male subjects. Values are Mean  $\pm$  SD (n = 200).

**Note:** n = Total number of subjects examined. Coffee drinker values are compared with non drinker control subjects.  
 \*p<0.005

**Table1:** Effect of coffee (cups/day) on liver function tests in Saudi normal male subjects. Values are Mean  $\pm$  SD, (n = 200).  
 n = Total number of subjects examined.

Coffee drinker values are compared with non drinker control subjects.

GROUPS	LIVER FUNCTION TESTS		
	ALT Iu / L	TB mg / dL	Ln (GGT)
Non Drinker	28.1 $\pm$ 25.9	1.06 $\pm$ 0.40	3.25 $\pm$ 0.68
Mild Drinker	27.9 $\pm$ 24.7	1.065 $\pm$ 0.43	3.22 $\pm$ 0.66
Moderate Drinker	27.6 $\pm$ 24.6	1.067 $\pm$ 0.44	3.21 $\pm$ 0.64
Heavy Drinker	27.2 $\pm$ 24.4	1.068 $\pm$ 0.46	3.22 $\pm$ 0.67

**Abbreviations:** ALT (Alanine aminotransferase), TB (Total bilirubin), Ln (GGT) (Natural logarithmic scale of gamma-glutamyltransferase).