Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/03f0md59

EFFECT OF COMBINED ANTI-RETROVIRAL THERAPY ON FASTING BLOOD SUGAR, CHOLESTEROL AND TRIGLYCERIDES: A FIVE-YEAR PROSPECTIVE STUDY IN A TERTIARY CARE INSTITUTE OF HIMACHAL PRADESH (INDIA)

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Abstract:
Background: The continuous rise in the number of individuals infected with Human Immunodeficiency Virus (HIV) each year remains a significant challenge to the survival of humanity. Patients infected with HIV who are undergoing implementation with cART experience adverse alterations in lipid and glucose metabolism, which coincide with the metabolic syndrome, resulting in a proatherogenic condition. "Antiretroviral medications could be influencing these metabolic changes. Adverse changes in glucose and lipid metabolism, lactic acidemia, bone dysfunctions, and unusual body fat distribution have been frequently observed as complications associated with HIV infection and potent antiretroviral therapy. [1]
Aims and Objectives: This study seeks to evaluate the impact of cART on fasting blood sugar, serum cholesterol, and triglyceride levels. This is set against the aim of minimizing complications and halting the progression to AIDS, thereby enhancing the quality of life for individuals affected by HIV/AIDS in alignment with the UN Sustainable Development Goals.
Materials and Methods: A total of 315 HIV patients were examined over a period of five years. Various models were chosen based on parameters including Fasting Blood Sugar, Cholesterol, and Triglycerides. The impact of different covariates, including gender, age, and the patient's ongoing adherence to treatment, was assessed for each of the models fitted. The evaluation of our study spanned six months and unfolded over five years.
Findings: Individuals diagnosed with HIV/AIDS must adhere to Antiretroviral therapy for life to effectively reduce the viral load, given the chronic and debilitating nature of the disease. This report highlights the ongoing presence of lipid abnormalities after the initiation of cART and emphasizes the importance of ongoing monitoring for individuals infected with HIV as they are more prone to hypertension and diabetes mellitus as compared to HIV seronegative population.

Keywords: Combined Anti-Retroviral Therapy (cART), Fasting Blood Sugar, Cholesterol, and Triglycerides, Public Health

INTRODUCTION

Combined Antiretroviral Therapy (cART) has significantly enhanced the prediction for individuals infected with the Human Immunodeficiency Virus, leading to a marked improvement in disease rates globally and a reduction in the progression to AIDS.[2-4] However, various clinical aspects have emerged alongside the increased lifespan of individuals living with HIV, primarily concerning certain chronic conditions or the use of cART. [5-6] Nucleoside reverse transcriptase inhibitors (NRTIs) have the potential to impact mitochondrial function, which may result in negative effects on adipose tissue and contribute to the development of lactic acidosis.[7-8] This could potentially result in myopathy, peripheral neuropathy, hepatic steatosis, and pancreatitis over time. [9-10]Even Efavirenz may result in metabolic disorders, along with dyslipidemia. The metabolic disorders observed during an infectious state are believed to be associated with cytokines.[11-12] Acquired immunodeficiency syndrome (AIDS) is distinguished by a heightened universality of hypertriglyceridemia and wasting. HIV triggers immune system activation and elicits an inflammatory response in various organs, including the walls of arteries, where it contributes to endothelial vessel injury. HIV also encourages dyslipidemia with increasing levels of triglyceride-rich lipoproteins and leads to obverse cholesterol transport. "cART worsens these dyslipidaemias by leading to hepatic steatosis, insulin resistance, lipogenesis and also malformation in adipocyte metabolism. Other factors which can contribute are differing classes of antiretroviral agents, age, and gender, duration of CART therapy, viral load, and CD4 count.[12-16]

Materials and Methods: Our study is an ongoing prospective cohort study of 317 homosexual, heterosexual, IV drug abusers, who were enrolled between January 2017 and November 2021. Briefly, our study followed a 6-monthly scheduled visit. Each visit included an interview, physical examination, and collection of blood samples. "Serum glucose, cholesterol and triglyceride lipid level measurements were included in the study protocol. Participants were required to fast for 8 hours before the visit to the study centre. Separate analytical panels were performed based on the fasting status of the participant". For this analytical study, we evaluated data which was collected up to November 21 from persons registered after 2017 to study changes in study parameters. Some patients did not adhere to treatment or died.

Enzymatic Assays: FBS tests are typically performed in clinical laboratories using automated analysers that employ these enzymatic methods. The blood sample is usually drawn after a period of fasting (8-12 hours). In India, fasting blood sugar (FBS) is generally calculated by the hexokinase method in clinical laboratories. This method is widely considered the gold standard for glucose measurement due to its specificity and accuracy. While other methods like glucose oxidase-peroxidase (GOD-POD) are also used, the hexokinase method is preferred for its dependability. The measurements were performed by the laboratory at IGMC Shimla. In India, cholesterol levels are primarily measured through enzymatic assays and calculated methods. Study assays, which are commonly used, involve a series of reactions that produce a coloured compound, with the intensity of the colour directly proportional to the cholesterol concentration. Calculated methods, such as the Fried Ewald formula, are utilized for estimating the LDL cholesterol based on total cholesterol level and triglycerides. Cholesterol oxidase-peroxidase (CHO-POD) is a common enzymatic method for measuring total cholesterol. Enzymatic assays are often coupled with spectrophotometry to quantify the color change, indicating cholesterol concentration. The Friedewald formula (LDL-C = Total Cholesterol - HDL-C - Triglycerides/5) is a commonly used method to estimate LDL cholesterol. This method is widely used due to its simplicity and the wide availability of data on total cholesterol and triglycerides. Data analysis: "The evaluation of changes in Fasting Blood Sugar, Cholesterol, and Triglycerides following the initiation of cART involved analyzing the values from the 5 years prior and after ART initiation for all 315 patients. "This analysis included the calculation of the standard error of the mean, standard deviation, and paired t-tests. "Over time, there have been shifts in physician practice and a rise in the use of lipid-lowering medications, leading to the establishment of a definition for elevated lipids concerning total cholesterol: specifically, total cholesterol levels exceeding 5.18 mmol/L. The TC threshold of 5.18 mmol/L (200 mg/dL) was chosen to align with the optimal target level ". [29].

Findings of the Population under investigation.
"A total of three hundred seventeen patients diagnosed with HIV fulfilled the criteria for the study. A total of 211 males were observed, with 111 individuals under the age of 40 and 100 individuals aged 40 and above."Among the total of 114 females, 65 were under the age of 40, while 49 were over the age of 40"."The median duration from pre-cART lipid level measurement to cART initiation was 0.26 years (interquartile range: 0.24–0.31 years)". Among these individuals, 99 had their first lipid measurement after cART within 0.5 years of starting cART, while 80 had a measurement taken between 0.5 and 1 year after cART initiation (32 individuals had measurements at both early time points). The standard characteristics of the study population, including males and females both above and below 40 years, are detailed in Table 1 and Figure 1 in the ANNEXURE.
Study Population 315
Age (years) 43.7 (7.1) 42.8 (7.0)
FBS 7.3 mmol/l "
Total cholesterol (mmol/L) 1.89 (1.16)"
"Triglycerides (mmol/L) 2.09 (1.93)"
Race Indian "
Values are mean (standard deviation) unless stated otherwise.
Repeated anova
Level of significance
"Two-factor ANOVA with repeated measures"
Null hypothesis"
"Alternative hypothesis"
'There is no significant difference between the groups of the first factor (measurement repetition) about the dependent variable. "
There is a significant difference between the groups of the first factor (measurement repetition) in the dependent variable.
"There is no significant difference between the groups of the second factor, Sex, about the dependent variable".
"There is a significant difference between the groups of the second factor, Sex, in the dependent variable". "
There is no interaction effect between the factor and Sex".

Key Findings:
FBS Data: Mean values show an increase from FBS1 (99.5 mg/dL) to FBS2 (107.7 mg/dL).Table 2 and Figure 2 in Annexure.
Periods of observation: Cholesterol: Significant increase from Cholesterol 1 (149.4 mg/dL) to Cholesterol 2 (168.6 mg/dL). Table 3 and Figure 3 in the Annexure.
Triglycerides: Moderate increase from TG1 (133.7 mg/dL) to TG2 (146.3 mg/dL). Table 4 and Figure 4 in the Annexure.
The scatter plots in the annexure enclosed show the correlation between before/after measurements, with the red diagonal line representing perfect correlation. Points above the line indicate increases, while points below show decreases.

CORRELATION ANALYSIS SUMMARY.As shown in the Annexure correlation matrix of medical variables.
STRONGEST CORRELATIONS (r>0.4):
1.Cholestrol1 vs Cholesterol 2: r=0.4749 (Strong Positive)
2.FBS 1vs FBS2: r=0.436 Strong Positive

MODERATE CORRELATIONS: ($0.3<r<0.4$)
TG1 vs TG2: =0.363 Moderate Positive
Cholesterol2 vs TG2: r= 0.349 (Moderate Positive)
3.Cholestrol 1 vs TG1 :0.338 (Moderate Positive)

WEAK BUT SIGNIFICANT POSITIVE CORRELATIONS
1. Age vs FBS1: = 0.250
2. Age vs TG2: =0.221
3. Age vs Cholesterol2: = 0.185

Clinical Interpretations
1.Before/after measurements show moderate consistency.
2. 2 Cholesterol and Triglycerides are positively correlated. Age shows a weak positive correlation with metabolic markers. All key correlations are statistically significant ($p < 0.05$)

KEY INSIGHTS
1. Before/After consistency: The strongest correlations are between baseline and follow-up measurements, with cholesterol showing the highest consistency (r=0.474)
2. Metabolic syndrome pattern: Cholesterol and Triglycerides show a positive correlation both at baseline and follow-up, suggesting metabolic syndrome clustering.
3. Age effects: Age shows weak but significant positive correlations with metabolic markers, particularly with follow-up measurements, indicating age-related metabolic changes.
4. Clinical Significance: All major correlations are statistically significant (p<.05>providing reliable evidence for these relationships.

Discussion
The initiation of cART in patients infected with HIV was linked to an increase in cholesterol, fasting blood sugar, and triglycerides. After 2 years of cART, peak levels were observed, with consistent increases noted over a 7-year follow-up period, as indicated by the optimal target of TC>5.18 mmol/L.Previosly studies conducted showed same findings of increase in blood sugar and hypertension.[17-18] The average level of TC was 1.12 mmol/L higher during the year 2–3 interval compared to the pre-cART baseline. The majority of the elevations in lipid levels emerged within the initial 0.5–1 years following the initiation of cART. [19-22]The results of this study align with clinical trials and existing data, including earlier analyses that showed an increase in serum cholesterol and triglycerides after the initiation of cART. This study presents an extended follow-up of a cohort of patients receiving cART treatment". The observed atherogenic lipid levels in these men, which emerged following the initiation of cART, reinforce the necessity for baseline and ongoing lipid assessments as a standard practice in the management of HIV treatment [23-24]. The extent to which serum lipid abnormalities influence the risk of cardiovascular events in individuals infected with HIV remains inadequately defined. A study involving 492 patients after a 5-year ART intervention reveals that their mean CD4 count rose from 315 to 550, reflecting an increase of 235. This indicates that nearly all participants experienced benefits from the cART. [25]The duration of the study encompasses a phase in which the understanding of lipid abnormalities linked to HIV and its treatment among physicians was advancing swiftly. Consequently, alterations in physician practice are apparent and pose a challenge for statistical accounting. We employed an optimal level for elevated lipids and modeling to consider lipid-lowering drug use; however, the available data do not allow for a complete assessment of the effects of these treatments.

Conclusions : This report highlights the ongoing presence of lipid abnormalities after the initiation of cART and emphasizes the importance of ongoing monitoring for individuals infected with HIV as they are more prone to hypertension and diabetes mellitus as compared to HIV seronegative population.

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Lipoprotein Phenotype Among HIV-1-Infected Men in the Multicenter AIDS Cohort Study. JAIDS Journal of Acquired Immune Deficiency Syndromes 48(3): p. 281-288, July 1, 2008. | DOI: 10.1097/QAI.0b013e31817bbbf0 6.

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Table 1: Male and female Above 40 years and less than 40 years

MALE		FEMALE	
BELOW 40 YRS	ABOVE 40 YRS	BELOW 40 YRS	ABOVE 40 YRS
111	100	65	49

Figure 1:

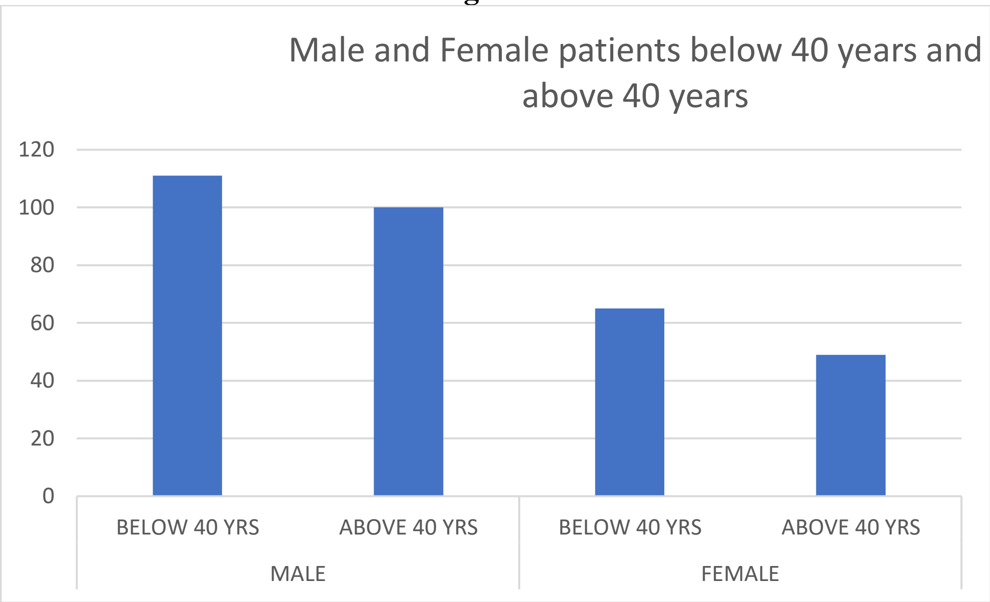


Table 2: Fasting blood sugar 1 and Fasting blood sugar 2 above and below 125mg/dl

FBS1		FBS2	
BELOW 125	ABOVE 125	BELOW 125	ABOVE 125
291	26	227	32

Figure 2:

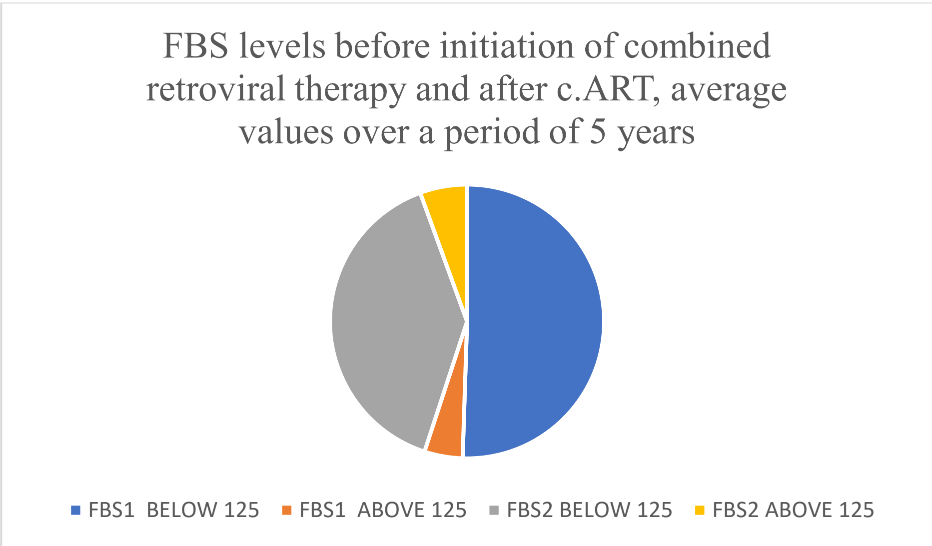


Table 3: Cholesterol levels 1 and Cholesterol levels 2 above and below 200mg/dl

Cholesterol 1		Cholesterol 2	
Below 200	Above 200	Below 200	Above 200
282	31	211	51

Figure 3:

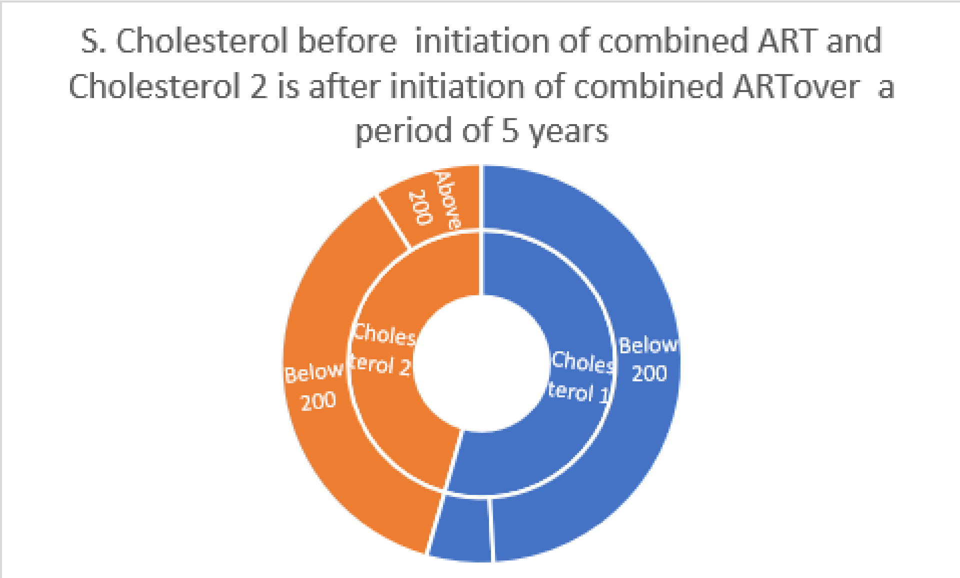


Table 4: Triglycerides 1 and Triglycerides levels above and below 150mg/dl

Triglycerides 1		Triglycerides 2	
below 150	above 150	below 150	above 150
227	81	168	94

Figure 4:

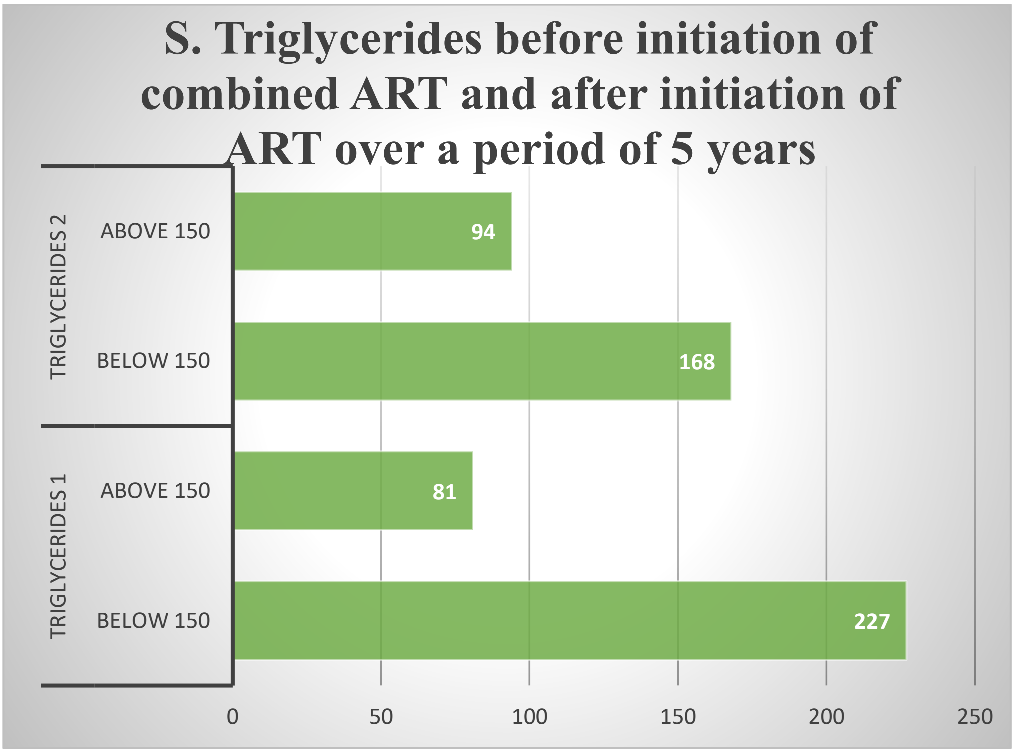


Figure 5:

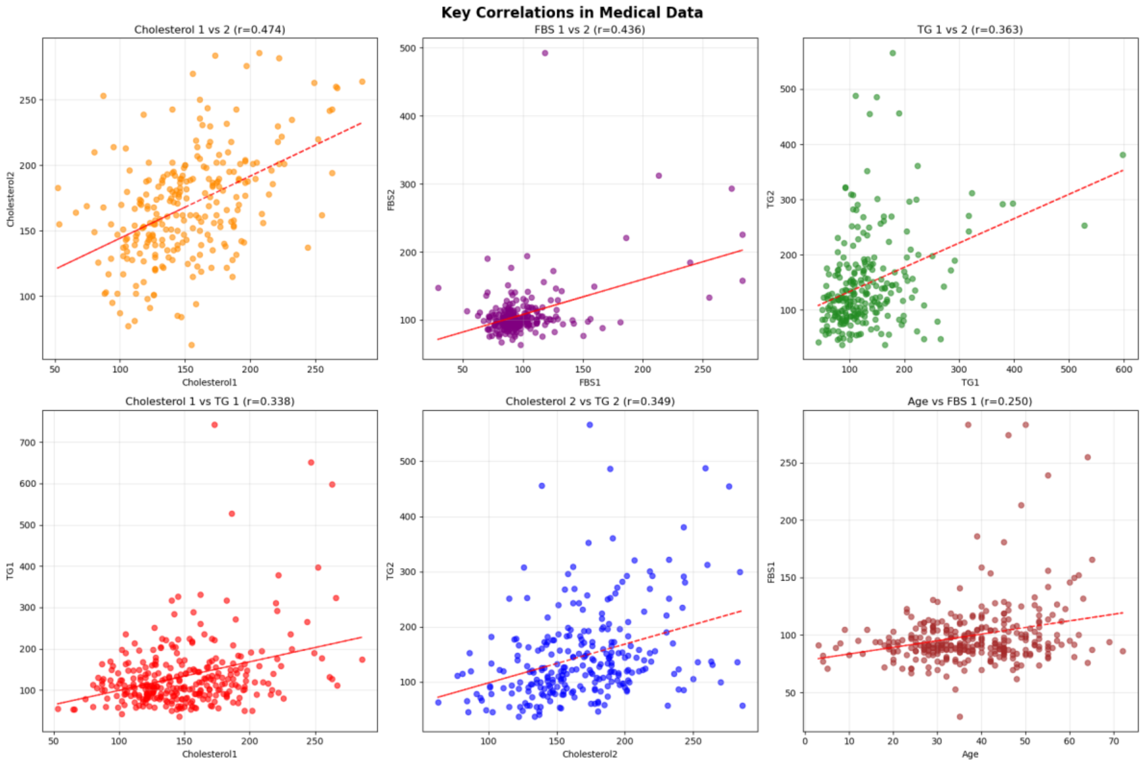


Figure 6:

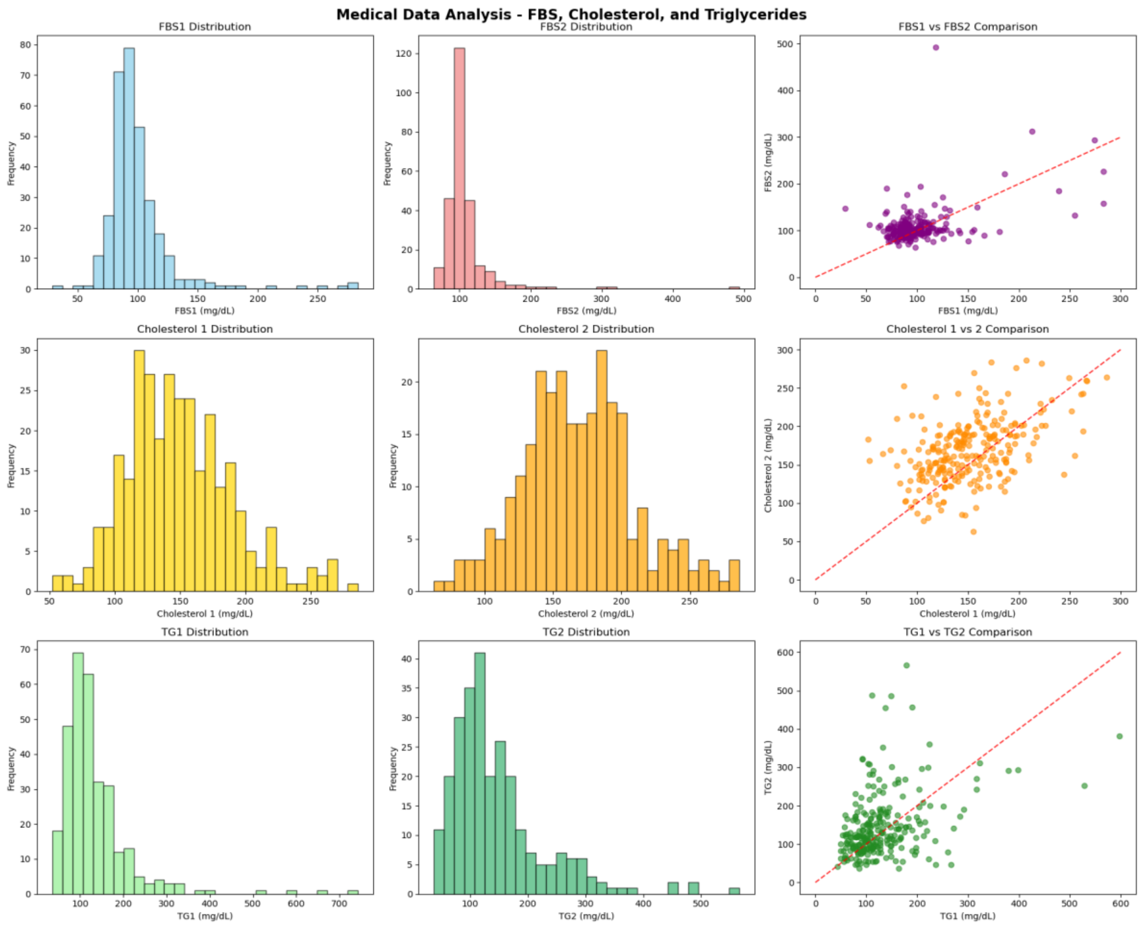
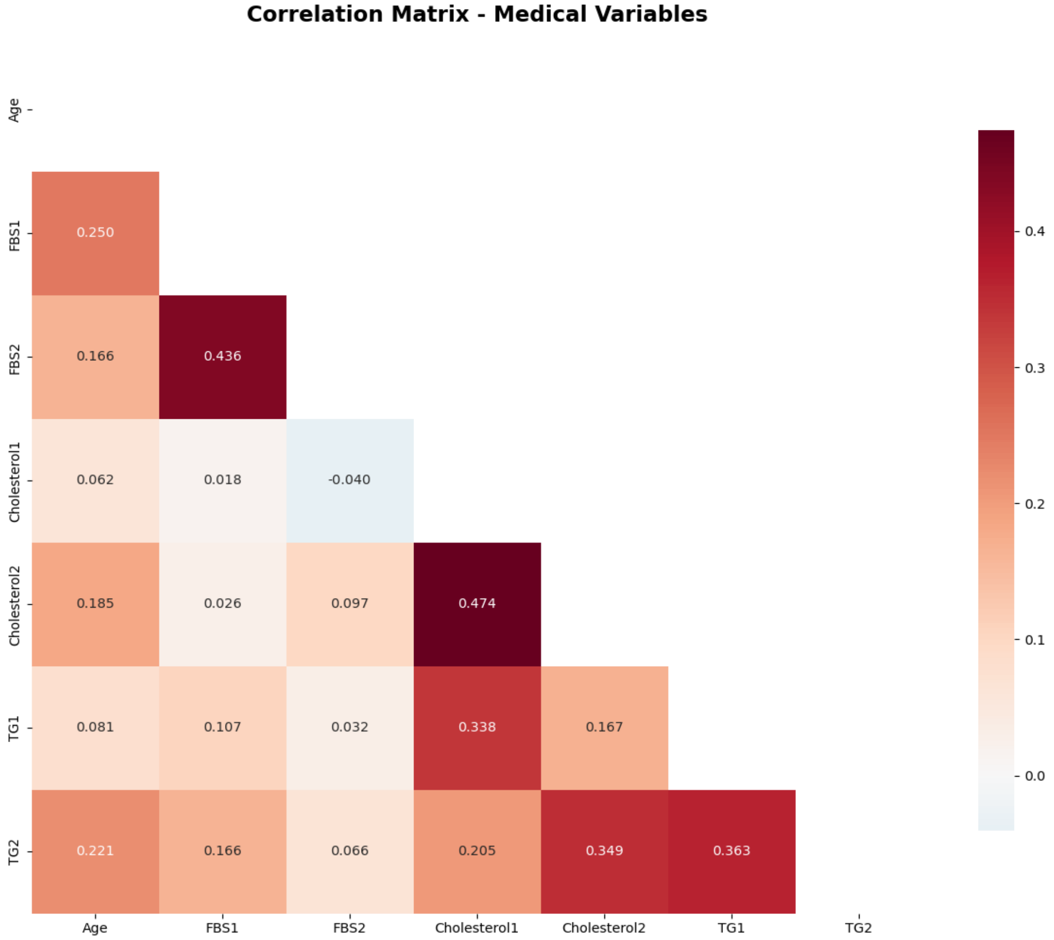


Figure 7:


Correlation Matrix - Medical Variables
Age
FBS1
FBS2
Cholesterol1
Cholesterol2
TG1
TG2
0.250
0.166
0.436
0.062
0.018
-0.040
0.185
0.026
0.097
0.474
0.081
0.107
0.032
0.338
0.167
0.221
0.166
0.066
0.205
0.349
0.363
Age
FBS1
FBS2
Cholesterol1
Cholesterol2
TG1
TG2
0.4
0.3
0.2
0.1
0.0