Serum Lipid Profiling In Highly Active Antiretroviral Therapy-Naïve HIV Positive Patients In Ghana; Any Potential Risk?

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Abstract

The human immunodeficiency virus (HIV) was unknown until the early 1980's and has since infected millions of persons in a worldwide pandemic. HIV infection results in relentless destruction of the immune system leading to the onset of acquired immunodeficiency syndrome (AIDS). The AIDS epidemic has resulted in the deaths of over half of its victims [1] with its etiologic agent, the human immunodeficiency virus (HIV) being one of the commonest lethal infections worldwide. The total number of infections in sub-Saharan Africa continues to increase because of poor resource availability and awareness regarding the disease [2].

The first reported cases of HIV infection in Ghana were recorded in 1986, mainly among women who had travelled outside the country. By the end of December 1999, a cumulative total of 37,298 cases had been recorded. Nearly 90% of the cumulative AIDS cases from 1986-1999 are between the age group of 15-49 years, with 63% of all reported cases being females. The female-to-male HIV/AIDS infection ratio is gradually attaining parity; changing from 6:1 in 1987 to approximately 2:1 in 1998. According to the 2007 HIV Sentinel Survey and National HIV Prevalence AIDS Estimates Reports, an estimated 264,481 people are living with HIV/AIDS out of which 110,666 are males and 153,815 are females [3].

The primary target of HIV infection is CD4+ lymphocyte because of the affinity of the virus to the CD4+ surface marker. HIV infection leads to progressive impairment of cellular functions, characterised by a gradual decline in peripheral blood CD4+ lymphocyte levels resulting in an increasing susceptibility to a wide range of opportunistic infections and certain malignancies [4].

Secondary infectious acute diseases have more evidently been associated with lipid abnormalities. These acute diseases can produce dyslipidaemia independent of the infective agent [5,6] and are mediated by different cytokines that regulate the immunological response to infection [7]. Hypertriglyceridaemia was the first dyslipidaemia to be reported in HIV infected patients with other lipid abnormalities such as hypocholesterolaemia or hypo HDL-cholesterolaemia also being reported [4]. Disorders of lipid metabolism have been described in patients with HIV infection before the introduction of HAART, including increased serum triglyceride (TG) levels and decreased cholesterol levels observed at various stages of HIV infection [8].

Considering the increasing incidence of HIV infection in Ghana and the fact that a number of infected patients will be put on HAART medication, this study was carried out to ascertain if any relationship existed between lipid profile and the different clinical stages of HIV infection and the potential risks, if any, it might pose to patients who were about to be enrolled on HAART medication.

Introduction

The human immunodeficiency virus (HIV) was unknown until the early 1980's and has since infected millions of persons in a worldwide pandemic. HIV infection results in relentless destruction of the immune system leading to the onset of acquired immunodeficiency syndrome (AIDS). The AIDS epidemic has resulted in the deaths of over half of its victims [1] with its etiologic agent, the human immunodeficiency virus (HIV) being one of the commonest lethal infections worldwide. The total number of infections in sub-Saharan Africa continues to increase because of poor resource availability and awareness regarding the disease [2].

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Considering the increasing incidence of HIV infection in Ghana and the fact that a number of infected patients will be put on HAART medication, this study was carried out to ascertain if any relationship existed between lipid profile and the different clinical stages of HIV infection and the potential risks, if any, it might pose to patients who were about to be enrolled on HAART medication.

**Methods**

One hundred and fifty (150) confirmed HAART naïve People Living with HIV/AIDS (PLWHAs) were included in this case control study. The subjects were recruited from the Central Regional Hospital (CRH) in Ghana between May to December 2008 and comprised of 88 (58.7%) males and 62 (41.3%) females. One hundred (100) healthy age and sex matched HIV-seronegative individuals were used as controls. PLWHAs were placed in three (3) groups according to the Centers for Disease Control and Prevention Criteria (CDC) classification system that emphasizes the importance of CD4+ T lymphocyte testing in clinical management of HIV-infected persons. Group 1: CD4 counts ≥500 mm⁻³; Group 2: CD4 counts between 200–499 mm⁻³; and Group 3: <200 mm⁻³.

**Sample collection**

Venous blood samples were collected into vacutainer® plain and EDTA tubes after an overnight fast (12-16 h) from the patients. The blood in the plain tubes were allowed to clot and spun at 3000rpm for 10 minutes and the serum was collected and stored at -80°C until assayed for biochemical parameters. The blood in the EDTA tubes were immediately used to estimate CD4 lymphocyte count.

**Assay**

Serum biochemistry was assayed using the ATAC® 8000 Random Access Chemistry System (Elan Diagnostics, Smithfield, RI, USA). The parameters that were assayed included Total Cholesterol (TC), Triglycerides (TG) and High Density Lipoprotein (HDL). Low Density Lipoprotein (LDL) was estimated using the Friedewald’s equation. The CD4+ lymphocyte count was estimated with the BD FACScount autoanalyzer system (Becton Dickinson, CA, USA).

**Statistical analysis**

The results are presented as mean ± standard error of mean (SEM). Statistical comparisons were analyzed using one way ANOVA and Bonferroni’s correction applied for multiple comparison tests. Correlations were evaluated using the Pearson’s correlation test statistic. For all statistical comparisons, the level of significance was set at $p<0.05$. All data analysis in this research was done using GraphPad Prism for Windows version 5.00 (GraphPad Software, San Diego, CA, USA).

**Results**

A summary of age, sex distribution and mean CD4 counts of controls and subjects are presented in Table 1. Out of the 150 subjects, males comprised 58.7% (88/150) with 54.5% (48/88) having CD4 counts <200 mm⁻³ whiles females comprised 41.3% (62/150) of the subjects with 51.6% (32/62) having CD4 counts <200 mm⁻³. A comparison of the mean age of the controls (38.76 ± 1.73 years) to the subjects (37.10 ± 0.84 years) showed no statistical significance likewise a comparison of the mean age of the controls classified by CD4 counts based on the CDC classification. The mean CD4 count of the control (1003.10 ± 77.53 mm⁻³) was significantly higher than that of the subjects (426.00 ± 19.17 mm⁻³) ($p<0.001$) and likewise when the subjects were classified into groups based on CD4 counts. An analysis of serum lipid profile parameters using one way ANOVA and Bonferroni’s correction for multiple comparison tests, showed decreases in serum Total Cholesterol ($F_{3,228}=384.8; p<0.001$), HDL-Cholesterol ($F_{3,228}=18.05; p$
<0.001) and LDL-Cholesterol (F<sub>3, 228</sub> = 48.10; p <0.001) as HIV infection progressed. Serum Triglycerides (F<sub>3, 228</sub> = 74.22; p <0.001) however increased with progression in HIV infection (Table 2). Correlation analyses revealed significant positive correlations between CD4 counts and TC (p <0.001), HDL-cholesterol (p <0.01) and LDL-cholesterol (p <0.01) while serum Triglycerides gave a significant negative correlation (p <0.001) to CD4 counts (Table 3).

**Discussion**

Previous studies have demonstrated that patients with AIDS exhibit highly abnormal total lipid concentrations in plasma [9]. Few authors [10, 11] who determined the levels of plasma triglycerides, total cholesterol and HDL cholesterol in HIV infected individuals by the level of immunological deficiency according to the CD4 lymphocyte count, also came to the same conclusion that, with an increase of immunological deficiency and clinical development of HIV infection, lipid profile disorders, indicated by an increase in triglyceride level and decreased concentrations of HDL cholesterol intensified as well. Consistent with earlier reports, this study also showed similar findings in which the decrease of CD4 count due to disease progression was accompanied by a decrease in total cholesterol, HDL cholesterol and LDL cholesterol, and an increase in triglyceride levels. The findings are also consistent with reports from Ducobu and Payen [10] who stated that HIV infection induced an early decrease of cholesterol and a late increase of triglyceride with a reduction of HDL. These changes were proportional to the lowering of CD4 count, which reflected the severity of infections, as was the case in this study. Shor-Posner et al., [12] reported similar findings in which they showed significantly low levels of total cholesterol, HDL, LDL cholesterol in HIV infected patients when compared to seronegative controls (P < 0.05). This low level of total, HDL, LDL cholesterol was reported to be associated with elevated levels of beta-2 microglobulin [4]. The low levels of cholesterol are prevalent even during early stages of HIV and were associated with a specific alteration in immune function [12]. The results of this study show that triglycerides increase in HIV positive patients at a late stage of disease. This hypertriglyceridaemia, found by other authors [13,14] is correlated to opportunistic infections and to interferon-α. The relationship between triglycerides (TG) and interferon-alpha (IFN-α) in HIV-positive patients has been previously found by Grunfeld et al., [8]. IFN-α may increase TG by two main mechanisms: a decrease in TG clearance; and an increase of de novo hepatic lipogenesis and VLDL production. This hepatic lipogenesis may be stimulated by three types of cytokines: tissue necrotic factor- alpha (TNF-α), Interleukin 1 and 6 (IL-1 and IL-6) that increase hepatic levels of citrate; and IFN-α that does not increase hepatic citrate. Both decreased TG clearance and increased hepatic VLDL overproduction have been found in HIV-positive patients, and the hepatic increased lipogenesis correlates to IFN-α [15]. Acute infections might increase TG by the way of hormones (steroids) or cytokines other than TNF-α or IFN-α. A decrease in cholesterol, especially in HDL-C occurs in HIV-positive patients long before hypertriglyceridaemia. These disturbances of cholesterol metabolism have been found by others [12,16]. TNF-α has been found to play a role in the peroxidation of plasma lipoproteins and lipids in experimental animals and in patients by stimulating the production of oxygen reacting species [17]. Lipid peroxidation may, in part, explain the alterations of cholesterol metabolism in HIV-positive patients and these modifications would have important implications in immune dysfunction.

Studies published until now show that dyslipidaemia in HIV-infected persons carries the same degree of cardiovascular risk as in HIV-negative population [18]. The plasma concentrations of triglyceride (TG) [19] and HDL-cholesterol have been considered independent risk factors for coronary artery disease [20,21], Stampfer et al. [22] in their study of triglyceride level and risk of myocardial infarction concluded that increased triglyceride level, small LDL particle diameter and decreased HDL-cholesterol levels appear to reflect underlying metabolic perturbations with adverse consequences for risk of myocardial infarction (MI); elevated triglyceride levels may help identify high-risk individuals.

**Conclusion(s)**

From the above findings, it is evident that HIV infection progression induces changes in serum lipid profile parameters which could be used to determine HIV infected persons with high risk of myocardial infarction before enrolment for HAART. All HIV-infected persons should therefore have their fasting plasma lipid profile prior to starting HAART with periodic repetitions after enrolling on HAART since significant increases in plasma TG and total cholesterol (TC) concentrations, often associated with abnormal body fat distribution and glucose metabolism alterations have been reported in HIV patients on HAART. Lipid profile
results can therefore be a good index for disease progression, intervention and management of HIV/AIDS patients in Ghana.

Acknowledgement(s)

We wish to express our profound gratitude to all PLWHAs who availed themselves voluntarily to participate in this research.

Authors Contribution(s)

CO and LQ carried out the biochemical analysis, CD4+ counts, performed the statistical analysis and drafted the manuscript. FAY designed the study and its coordination and participated in the drafting of the manuscript. All authors read and approved the final manuscript.

References


Illustrations

Illustration 1

Table 1: Age, Sex distribution and mean CD4 counts of controls and subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Subjects</th>
<th>&gt;500</th>
<th>200-499</th>
<th>&lt;200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years)</td>
<td>38.76 ± 1.73</td>
<td>37.10 ± 0.84</td>
<td>38.72 ± 2.58</td>
<td>37.43 ± 1.57</td>
<td>36.68 ± 1.08</td>
</tr>
<tr>
<td>Males (%)</td>
<td>63</td>
<td>88 (58.7)</td>
<td>17 (19.3)</td>
<td>23 (26.1)</td>
<td>48 (54.5)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>37</td>
<td>62 (41.3)</td>
<td>9 (14.5)</td>
<td>21 (33.9)</td>
<td>32 (51.6)</td>
</tr>
<tr>
<td>CD4 count (mm³)</td>
<td>1003.10 ± 77.53</td>
<td>426.00 ± 19.17***</td>
<td>732.10 ± 55.75††</td>
<td>306.70 ± 17.44†††</td>
<td>185.30 ± 80.53^^^</td>
</tr>
</tbody>
</table>

*P<0.05. **P<0.01. ***P<0.001 defines the level of significance when control was compared to subjects; †P<0.05. ††P<0.01. †††P<0.001 defines the level of significance when control was compared to subjects (CD4 ≥500); †‡P<0.05. ††‡P<0.01. †††‡P<0.001 defines the level of significance when control was compared to subjects (CD4 200-499); †^P<0.05. ††^P<0.01. †††^P<0.001 defines the level of significance when control was compared to subject (CD4 ≥500).
Table 2: Effect of HIV progression on Lipid Profile Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Test subjects</th>
<th>&lt;200</th>
<th>200-499</th>
<th>≥500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>5.21±0.10</td>
<td>2.43±0.05***</td>
<td>2.14±0.46</td>
<td></td>
<td>2.64±0.46††</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.98±0.05</td>
<td>1.83±0.03***</td>
<td>1.90±0.41</td>
<td></td>
<td>1.81±0.35††</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>1.38±0.05</td>
<td>1.05±0.04***</td>
<td>0.90±0.41</td>
<td></td>
<td>0.97±0.42</td>
</tr>
<tr>
<td>(mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>1.65±0.05</td>
<td>1.02±0.03***</td>
<td>0.96±0.38</td>
<td></td>
<td>0.91±0.40††</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001 defines the level of significance when control was compared to subjects; †P<0.05, ††P<0.01, †††P<0.001 defines the level of significance when control was compared to subjects (CD4 <200); †P<0.05, ††P<0.01, †††P<0.001 defines the level of significance when control was compared to subjects (CD4 200-499); ^P<0.05, ^^P<0.01, ^^^P<0.001 defines the level of significance when control was compared to subject (CD4 ≥500)
Table 3: Pearson's correlation coefficients of biochemical parameters for subject group (upper right)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CD4</th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 (mm³⁻¹)</td>
<td>0.67***</td>
<td></td>
<td>-0.27**</td>
<td>0.27**</td>
<td>0.21**</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>0.07</td>
<td>-0.18</td>
<td>0.16*</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>-0.18</td>
<td>0.10</td>
<td>-0.31</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>-0.20</td>
<td>0.02</td>
<td>-0.20</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>0.01</td>
<td>0.11</td>
<td>0.08</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

* Correlation is significant at the level 0.05. ** Correlation is significant at the level 0.001. *** Correlation is significant at the level 0.0001. HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, CD: Cluster of differentiation, TC: Total Cholesterol, TG: Triglycerides
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