Is gamma glutamyl transferase a diagnostic marker of prostate disease?

Adekola S.A\(^1\), Popoola O.A\(^2\), Ogundiran S.M\(^3\), Oparinde D.P\(^4\), Onuegbu A.J\(^5\)

\(^1\)Department of Chemical Pathology, University of Ibadan, Nigeria. \(^2\)Genetic and Bioethics Research Unit, Institute for Advance Medical Research and Training, College of Medicine, University of Ibadan, Nigeria. \(^3\)Department of Chemical Pathology, University College Hospital, Ibadan, Nigeria. \(^4\)Department of Chemical Pathology, Ladoke Akintola University Teaching Hospital, Osogbo, Nigeria. \(^5\)Department of Chemical Pathology, Nnamdi Azikiwe University, Awka, Nigeria.

*Corresponding author: popoolaolayiwola@yahoo.com

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ABSTRACT

Background: Early diagnosis, detection and treatment have been one of the main goals of reducing the mortality from benign prostatic hyperplasia (BPH) and prostate cancer (PCA). The most common used screening and diagnostic tool for this condition is serum prostate specific antigen (PSA) level. Since PSA is synthesized by other tissues besides the normal and tumor prostate cells, the specificity of PSA as a biomarker for BPH and PCA has been called into question and may be improved. Therefore, other markers of this disease condition are being sought. Since gamma glutamyl transferase GGT is prominently expressed in prostate, we hypothesize that an increase in GGT occurs during prostate enlargement, and that GGT could be appropriate as a novel biomarker for BPH and PCA. Aim: To determine the serum levels of GGT in subjects with BPH and prostate cancer and compare these results with the concentrations of established biomarkers of prostate cancer such as PSA and MDA. Methods: A total number of 30 male subjects with BPH, 30 with prostate cancer and 30 age-matched controls were recruited for the study. Result: There was no significant difference in mean GGT levels between the patient (BPH and PCA) and control group. Similarly, there was no correlation between Serum MDA, GGT and PSA amongst the groups studied. Conclusion: Our findings provide evidence that GGT is not a sensitive and specific marker for detection of either BPH or prostate cancer.

Keywords: PSA, Prostate cancer, BPH, gamma glutamyl transferase

INTRODUCTION

Prostate cancer is the commonest cancer among Nigerian males and the specific cause remains unknown.\(^1\) Risk factors for prostate cancer include age, genetics, race, diet, lifestyle, nationality, family history, infection and inflammation of the prostate and other factors.\(^2\) Benign prostatic hyperplasia (BPH) is a non-cancerous growth of prostate tissue.\(^3\) The chance of developing BPH increases with age.\(^4\) More than half of men over 60 have BPH and about 80 percent have BPH by age 80.\(^4,5\)
Symptoms of BPH include restricted, weak, or intermittent urine flow, leakage after urination, a feeling of being unable to empty the bladder completely, urinary frequency or urgency. 

Prostate cancer is uncommon in males less than 45 years, but becomes more common with advancing age; the average age of diagnosis is 70 years. Autopsy studies of Chinese, German, Israeli, Jamaican, Swedish and Ugandan who died of other causes have found prostate cancer in 30% of men in their 50s and in 80% of men in their 70s. In 2005 in the United States, there were an estimated 230,000 new cases of prostate cancer and 30,000 deaths due to prostate cancer. 

Prostate cancer is usually diagnosed by digital rectal examination (DRE) and prostate specific antigen (PSA). Prostate-specific antigen (PSA), is a protein enzyme (serine protease) produced by the prostate. Since the introduction of PSA screening 25 years ago, prostate cancer diagnosis and management have been guided by this biomarker. Although serum PSA measurement is regarded as the best conventional tumor marker available, there is little doubt that it has great limitations. High grade prostate cancer is not rare among men with PSA levels generally thought to be in the normal range (4.0ng/mL or less). The threshold above which biopsies are indicated has decreased to a serum PSA value of 3ng/mL, which results in a negative biopsy rate of 70 to 80%. It is estimated that about 50% of newly diagnosed cases of prostate cancer using PSA screening are unlikely to manifest clinically. PSA was initially thought to be solely synthesized by epithelial cells of the prostate and thus was used as a biomarker for diagnosing and management of prostate cancer. However, PSA has also been found in a variety of other normal and tumor cell types and has been isolated from the biological fluids synthesized by numerous cells, although PSA is mainly synthesized by prostatic epithelial cells. 

Gamma glutamyl transferase (GGT) level are commonly used as a biological marker for excessive alcohol consumption and as an index of liver damage, but recent data suggest that they can also be used as a marker of oxidative stress. However, high levels of GGT are present in the prostate and this may account for the fact that the activity of GGT in sera of males is higher than in sera of females. Therefore, prostatic malignancy might be a source of elevated GGT activity in sera. 

The role of oxidative stress has been postulated in many conditions such as cancers, autoimmune disease, and atherosclerosis. Oxidative stress, arising as a result of an imbalance between free radical production and antioxidant defense, is associated with damage to a wide range of molecular species including lipids, protein and nucleic acid. MDA is an end-product derived from peroxidation of polyunsaturated fatty acids and related esters. In contrast to free radicals, aldehydes are relatively stable and therefore able to diffuse within or out of the cell and to attack targets distant from the site of original free-radical initiation.

**METHODOLOGY**

The study consists of 90 male subjects, 30 controls, 30 BPH subjects and 30 subjects with carcinoma of the prostate. The age range of cases (BPH and PCA) was matched with controls. Informed consent was obtained from all participants. Patients that take alcohol and those that have a history of liver disease were excluded from the study. Five ml of blood were drawn from subjects and controls and placed into plain bottles. The samples were allowed to clot and separated after centrifugation at 3,000 rpm for five minutes into a plain bottle. Serum samples were stored at -20°C until the time for analysis. Serum levels of GGT were estimated using commercial kit based on enzymatic kinetic method from Agape Diagnostic laboratory UK. Serum Malondialdehyde (MDA) was estimated using Thiobarbituric acid reacting substance method (TBARS). The principle of TBARS rely on the ability of Trichloroacetic acid (TCA) to precipitates protein and thiobarbituric acid reacts with MDA (malondialdehyde) to give a red colored complex that is read spectrophotometrically (Biorad SmartSpec™ plus) at 532nm. Serum PSA level was assayed using kits based on Enzyme immunoassay (ELISA) method from Teco Diagnostic laboratory, USA.

**Statistical analysis**

Data were analysed using Microsoft office Excel 2007 and SPSS version 16. Results were reported as mean ± SD and pearson’s correlation was used to determine the
relationship between MDA, PSA and GGT. The level of significance was set at \( p < 0.05 \).

**RESULT**

Table 1: Comparison of Mean ±2 SD of parameters in subjects and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BPH N=30</th>
<th>Prostate cancer N=30</th>
<th>Control N=30</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>66.67± 11.55</td>
<td>68.50± 10.31</td>
<td>64.23± 11.31</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>60.90± 10.18</td>
<td>63.85± 7.09</td>
<td>61.43± 6.89</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>23.67± 4.01</td>
<td>24.35± 6.02</td>
<td>22.40± 2.82</td>
<td>NS</td>
</tr>
<tr>
<td>MDA(µmol/ml)</td>
<td>1.67± 0.82*</td>
<td>1.55± 1.27**</td>
<td>0.06± 0.18</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>35.53± 19.83</td>
<td>33.81± 12.34</td>
<td>29.50± 10.64</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>PSA(n g/ml)</td>
<td>22.77± 22.35*</td>
<td>70.25± 50.40**</td>
<td>0.75± 1.07</td>
<td>( p &lt; 0.01 )</td>
</tr>
</tbody>
</table>

NS: Not significant  
* significance between BPH and control  
** significance prostate cancer and control

There was no significant difference in mean age when BPH, prostate cancer patients and controls were compared (66.67±11.55years, 68.50±10.31years and 65.23±11.31years respectively, \( p > 0.05 \)). Similarly, the difference in mean BMI among the groups was not significant (BPH 23.67±4.01 Kg/m², PCA 24.35±6.02 Kg/m² and control 22.40±2.82 Kg/m² respectively \( p > 0.05 \)). However, there was a significant difference in mean MDA between BPH and prostate cancer patients, versus control (1.67±0.82 µmol/ml, 1.55±1.27 µmol/ml and 0.06±0.18 µmol/ml respectively, \( p < 0.05 \)) (Table 1).

A difference in mean GGT was recorded when the control group was compared with the BPH group and the prostate cancer group (Figure 1), but the difference was not significant (BPH 35.53±29.83 U/L, PCA 33.81±12.34 U/L and controls 29.50±10.64 U/L respectively, \( p > 0.05 \)). Mean serum PSA was significantly higher in prostate cancer patients when compared with subjects originating from BPH and controls (70.25±50.40 ng/ml, 22.77±22.35ng/ml and 0.75±0.17 ng/ml respectively, \( p < 0.01 \)).

**DISCUSSION**

In our study, the lipid peroxidation product (MDA) was significantly higher in the two test groups (BPH and PCA) compared to those in the control group. Similar reports of increased MDA in prostate cancer patients have been documented.[19,20] Levels of MDA are often used as an index of lipid peroxidation caused by free radicals which have been implicated in the pathogenesis of many diseases involving different organs including the prostate. The result of our study was further supported by the result of a recent study, where a higher level of MDA was observed in BPH when compared with controls.[17] Data generated from this study support the idea that free radical generation play an important role in carcinogenesis. The increased MDA is an evidence of increased oxidative stress in BPH and prostate cancer and this suggests that antioxidants may have a protective role in Prostate cancer.
An increased serum concentration of PSA was observed in prostate cancer and BPH when compared with controls. Our result shows that PSA is a more sensitive marker for prostate cancer and BPH than GGT and that its efficient use might require an ethnic and age specific reference range to be established in Nigeria.

Contrary to the fact that higher circulating GGT in men is from the prostate and a view that with increase in size and activity of the prostate during BPH and prostate cancer, no significant increase in mean serum GGT was observed when patients with BPH and prostate cancer were compared with controls (Figure1). One of the goals of this study was to determine whether GGT can be used as a marker in BPH and prostate cancer; however our findings have shown that despite high levels of GGT in prostate it cannot be a sensitive marker of the two disease conditions. Although there is evidence that GGT is a sensitive marker for metastatic renal carcinoma.[21] Our results seem to suggest that there is no increased production of prostatic GGT during BPH and prostate cancer.[11]

There was a fairly strong negative correlation between MDA and GGT in prostate cancer, however this was not statistically significant. This tends to suggest that a higher level of free radicals in the circulation of patients with BPH and prostate cancer tend to suppress the release of GGT especially from the prostate.

**CONCLUSION**

Our findings have shown that GGT is not an appropriate diagnostic marker for the two disease conditions despite its increased activity in men. However, our results shows a marginal increase in production of GGT in BPH and prostate cancer subjects when compared with controls.

### Table 2: MDA, GGT and PSA in prostate cancer, BPH patients and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prostate Cancer (r)</th>
<th>p-value</th>
<th>BPH (r)</th>
<th>p-value</th>
<th>Control (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA vs. GGT</td>
<td>-0.41</td>
<td>0.72</td>
<td>-0.06</td>
<td>0.754</td>
<td>-0.03</td>
<td>0.873</td>
</tr>
<tr>
<td>MDA vs. PSA</td>
<td>0.07</td>
<td>0.763</td>
<td>-0.02</td>
<td>0.898</td>
<td>-0.22</td>
<td>0.250</td>
</tr>
<tr>
<td>GGT vs. PSA</td>
<td>0.05</td>
<td>0.983</td>
<td>0.11</td>
<td>0.547</td>
<td>0.14</td>
<td>0.448</td>
</tr>
</tbody>
</table>

There was a fairly strong negative correlation between MDA and GGT in patients with prostate cancer, which was not significant (r = -0.41, p = 0.72). There was no significant correlation between MDA and PSA, GGT and PSA in prostate cancer, BPH patients and control.

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Conflict of Interest: None declared

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