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Plasma Beta-Glucuronidase Activity: A Novel Tool to Distinguish Type 1 from Type 2 Amiodarone-Induced Thyrotoxicosis?

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Keywords
Amiodarone-induced thyrotoxicosis · Beta-glucuronidase · Plasma beta-glucuronidase activity · Destructive thyroiditis

Abstract
Background: Amiodarone-induced thyrotoxicosis (AIT) is a common and deleterious side effect of amiodarone use. There are two types of AIT, characterized by distinct pathogenic mechanisms and, hence, different treatments. Discriminating between type 1 (AIT1) and type 2 (AIT2) AIT is often very challenging. Beta-glucuronidase (β-G) is a lysosomal enzyme released into the extracellular fluid during inflammation. ***Objectives:*** To examine whether the determination of the plasma activity of β-G is useful in distinguishing AIT1 from AIT2. ***Methods:*** The study included 67 subjects: 9 with AIT1, 9 with AIT2, 14 with hyperthyroidism due to Grave's disease or toxic multinodular goiter, 14 with subacute thyroiditis, and 21 euthyroid controls. Thyroid function tests and plasma β-G activity were determined in all participants, while thyrotoxic patients also underwent thyroid ultrasound/scintigraphy and urine iodine excretion assessment. ***Results:*** Plasma β-G activity (expressed as mean ± SD in nmol 4-methylumbelliferone [4-MU]/mL plasma/h) in AIT2 was higher compared to AIT1 (2,263.6 ± 771 vs. 1,101.8 ± 201.9, $p < 0.05$) and similar to subacute thyroiditis (2,263.6 ± 771 vs. 2,083.2 ± 987.5, p = ns). β-G activity did not differ significantly between AIT1 and controls (1,101.8 ± 201.9 vs. 954.6 ± 248.6, p = ns). ROC curve analysis revealed that β-G activity had a high predictive value for destructive processes, namely AIT2 and subacute thyroiditis (AUC 0.846, 95% CI 0.748–0.943) and a cut-off value of 1,480.5 nmol 4-MU/mL plasma/h was able to discriminate between destructive and non-destructive thyroid conditions with 74% sensitivity and 82% specificity. ***Conclusion:*** In our study, plasma β-G activity performed well in distinguishing AIT1 from AIT2. Further studies are warranted to establish its usefulness as a discriminator between the two AIT types.

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Introduction

Amiodarone-induced thyroid dysfunction, either hypothyroidism (AIH) or hyperthyroidism – thyrotoxicosis (AIT), affects up to 20% of amiodarone-treated patients [1]. Two types of AIT exist and they are characterized by distinct pathogenic mechanisms: type 1 (AIT1) is a form of iodine-induced hyperthyroidism in response to the high iodine load present in amiodarone, while type 2 (AIT2) is a drug-induced destructive thyroiditis. There are also mixed forms, in which both pathogenic mechanisms contribute to thyroid dysfunction [2]. Thionamides is the treatment of choice in AIT1, while AIT2 is treated with oral glucocorticoids [3]. Although the diagnosis of thyrotoxicosis is easy, based on the findings of increased thyroid hormone concentrations and suppressed TSH levels, discrimination between AIT1 and AIT2 in order to select the appropriate treatment is often challenging. AIT1 involves excessive thyroid hormone synthesis by autonomously functioning thyroid tissue, which typically occurs in the context of pre-existing multinodular goiter or latent Grave's disease (GD), while AIT2 usually affects an apparently normal thyroid gland [1]. Positive thyroid auto-antibodies point to AIT1, but their presence or absence should not be used in isolation to rule in/out either form of AIT [4]. Color flow Doppler sonography (CFDS) shows increased vascularity in AIT1, whereas it shows absent hypervascularity in AIT2 [5]. Thyroid radioactive iodine uptake values are variable in AIT1 and suppressed in AIT2 [6]. Serum levels of interleukin-6 (IL-6) have been used as a marker of thyroid inflammation and high levels may support the diagnosis of AIT2, but poor specificity and high cost limit its routine use [7, 8].

Beta-glucuronidase (β-G) is an enzyme normally expressed in the lysosomes of cells and is responsible for catalyzing the hydrolysis of glycosaminoglycans, thus participating in the degradation of extracellular matrix components [9]. During inflammation, β-G is released from lysosomes to the extracellular fluid, either as a result of tissue damage or as a secretory product of white blood cells [10]. In fact, increased activity of β-G has been detected in several body fluids of patients suffering from bacterial infections [11–13].

To the best of our knowledge, β-G has never been studied in thyroid disease. The aim of this study was to investigate whether plasma levels of β-G activity could be used as a novel marker to discriminate between AIT1 and AIT2. We hypothesized that plasma activity of β-G is increased in AIT2, which is a destructive thyroiditis, but not in AIT1, whose pathogenesis does not involve inflammation. Herein, we showed for the first time that β-G activity is increased in AIT2 compared to AIT1.

Materials and Methods

Patients and Study Design

The initial study population consisted of 71 subjects. Serum and plasma samples were collected from all participants for thyroid function tests including TSH, total T3 and T4, and thyroid autoantibodies (anti-thyroid peroxidase-AbTPO and anti-thyroglobulin-AbTG), as well as β-G activity determination. All samples were immediately stored at –80 °C until analysis. Blood samples were also collected for erythrocyte sedimentation rate and C-reactive protein (CRP) evaluation; the latter were processed immediately. Thyrotoxic patients were assessed in the acute phase of hyperthyroidism and all measurements were carried out before the initiation of any treatment. The individuals were divided in five groups as follows: out of the 22 consecutive cases of AIT included in the study, 9 were diagnosed with AIT1 ($Group_{AIT1}$), 9 with AIT2 ($Group_{AIT2}$), and 4 could not be readily classified to either AIT1 or AIT2 based on the criteria mentioned below; these patients were considered to suffer from "mixed" forms of AIT and were therefore excluded from the analysis. $Group_{GD/TMNG}$ ($n = 14$): patients suffering from active GD or toxic multinodular goiter (TMNG), who had never used amiodarone. $Group_{ST}$ ($n = 14$): patients diagnosed with subacute thyroiditis, who had never used amiodarone. $Group_{Control}$ ($n = 21$): euthyroid subjects, without history of thyroid disease or amiodarone use, with normal levels of thyroid function tests. Thyroid imaging was performed in hyperthyroid subjects and included ultrasound examination with CFDS, as well as thyroid ^{99m}Tc-pertechnetate scintigraphy. Urinary iodine excretion (UIE) was also assessed.

Thyrotoxicosis was diagnosed in subjects presenting symptoms and signs of hyperthyroidism, as well as suppressed TSH and increased T4 and/or T3. The diagnosis of AIT additionally required current amiodarone use, spanning at least 2 months. AIT1 was diagnosed when all of the following were present: (1) increased thyroid volume or nodular composition on ultrasound, (2) increased vascularity at CFDS (patterns I–III), (3) normal or increased tracer uptake on ^{99m}Tc-pertechnetate scintigraphy. The concurrent existence of the following criteria was obligatory to diagnose AIT2: (1) normal or slightly increased thyroid volume without nodules, (2) absent hypervascularity on CFDS (pattern 0), (3) no thyroid visualization at ^{99m}Tc-pertechnetate scintigraphy, (4) absence of circulating thyroid autoantibodies. Cases of AIT that could not be readily assigned to AIT1 or AIT2 group according to the above criteria (i.e., mixed forms) were excluded from the study. The diagnosis of GD was based on the detection of increased titers of thyroid autoantibodies in individuals with enlarged thyroid/increased vascularity at ultrasound and diffusely increased tracer uptake on scintigraphy. TMNG was diagnosed when a multinodular thyroid appearance co-existed with heterogeneously increased tracer uptake on scintigraphy. Finally, a painful thyroid, increased erythrocyte sedimentation rate, thyroid heterogeneity at ultrasound, and absent visualization on scintigraphy were the diagnostic criteria of patients with subacute thyroiditis.

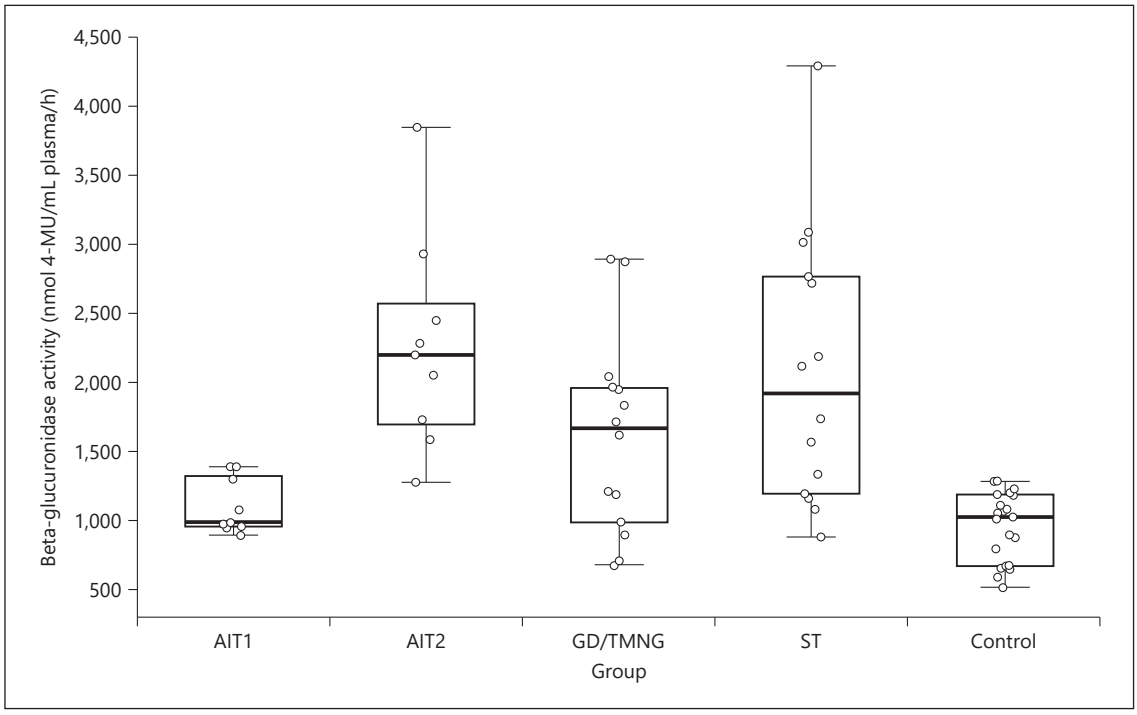


Fig. 1. Box plot of plasma beta-glucuronidase activity for each one of the study groups. Small circles: each individual's value. Rectangle: 25th–75th percentile. Horizontal line within the rectangle: median. Whiskers: minimum and maximum.

The subjects included in our study had no history of liver disease, chronic inflammatory conditions, or malignancy and were not on any medication known to affect the immune system. Furthermore, they presented no sign of acute inflammation on clinical examination (with the exception of patients with subacute thyroiditis). All participants provided written informed consent and the study was approved by the University Hospital of Patras Ethics Committee.

Hormone Measurements

All assays for hormone determinations were performed by electrochemiluminescence quantization (Elecsys 2010, Roche Diagnostics, Laval, Quebec). Normal range for each of the parameters studied was as follows: TSH: 0.27–4.2 mIU/L, T4: 5.1–14.1 μg/dL, T3: 0.8–2.0 ng/mL, AbTPO: <34 IU/mL, AbTG: <115 IU/mL, TRAb: <2 IU/L. The intra-run and inter-run coefficient of variance values were 3.4–4.2% and 3.3–7.2% for TSH, 1.1–3.0% and 3.7–4.5% for T4, 1.5–3.1% and 1.3–1.7% for T3, 2.7–6.3% and 4.2–9.5% for AbTPO, and 1.3–4.9% and 2.1–6.3% for AbTG.

Beta-Glucuronidase Assay

Levels of β-G activity were determined in human plasma samples using 4-methylumbelliferyl-β-D-glucuronide as substrate, as previously described [12, 14]. β-G activity was expressed as nmol 4-methylumbelliferone (4-MU)/mL plasma/h.

Urine Iodine Excretion

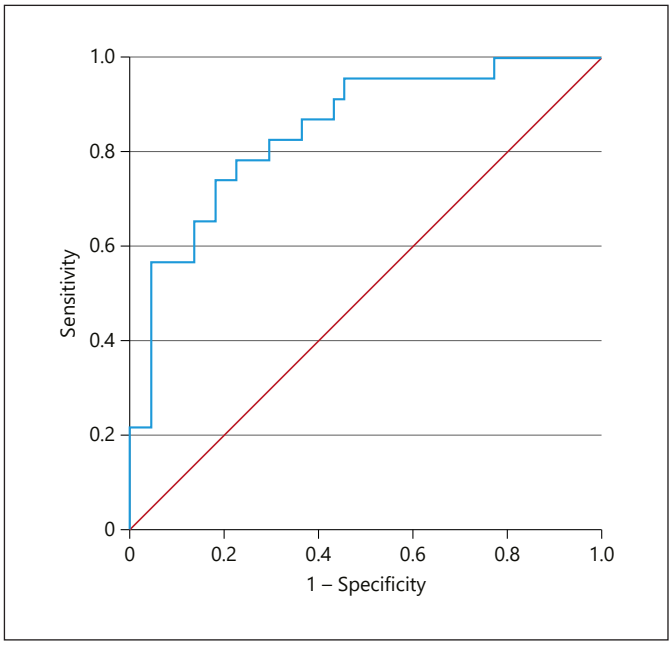
Urine iodine was measured twice in spot samples collected on two different days and the mean value was used. A photometric method (Sandell-Kolthoff reaction) was employed to determine UIE [15]. Our laboratory is taking part in an external evaluation program for UIE determination conducted by the EQUIP Program (Atlanta, GA, USA).

Thyroid Imaging

Thyroid ultrasound as well as CFDS was performed using a 10-MHz linear array transducer (GE Logiq V5 Expert L6-L12RS, GE Healthcare, Chicago, IL, USA). Thyroid scintigraphy was conducted 30 min after intravenous administration of 150 MBq of ^{99m}Tc.

Statistical Analysis

Parameters were tested for normality. Comparisons between the different groups were performed using one-way ANOVA, while Tamhane's test was used for post-hoc analysis. Receiver operating characteristics (ROC) curve and area under the curve (AUC) were calculated to assess the ability of β-G activity to discriminate between destructive (AIT2 and subacute thyroiditis) and non-destructive (AIT1, GD, TMNG, and controls) conditions. The maximum sum of sensitivity and specificity was used to determine the optimum cut-off value for β-G activity. A p value of less than 0.05 was considered statistically significant. All statistical procedures were performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The visualization tools of BioVinci version 1.1.5 (developed by BioTuring Inc., San Diego, CA, USA) were also used.



Color version available online

Fig. 2. ROC curve of beta-glucuronidase activity. AUC, area under the curve; CI, confidence intervals. AUC 0.846 (95% CI 0.748–0.943).

Results

Our study included 67 subjects with a mean age of 55.2 years (range: 25–80 years). There was no statistically significant difference between the subgroups regarding the age, gender, and body mass index (BMI). Duration of amiodarone use in patients with AIT ranged from 2 to 40 months (mean: 11.5 months, median 6 months). UIE was invariably >600 μg/L (upper limit of detection in our laboratory) in all AIT patients, while median UIE was 105.6 μg/L (range: 34.5–405.9 μg/L) in the rest of our thyrotoxic patients. Erythrocyte sedimentation rate and CRP levels were high in all patients of $Group_{ST}$, but within normal range in the rest of the study participants.

β-G activity (nmol 4-MU/mL plasma/h) for each group of subjects is shown in Figure 1. Analysis of variance showed that β-G activity was different among the five groups ($p < 0.0001$) and post-hoc analysis revealed statistically significant difference between the following pairs: $Group_{AIT1}$ versus $Group_{AIT2}$ (mean ± SD: 1,101.8 ± 201.9 vs. 2,263.6 ± 771, $p < 0.05$), $Group_{AIT1}$ versus $Group_{ST}$ (1,101.8 ± 201.9 vs. 2,083.2 ± 987.5, $p < 0.05$), $Group_{Control}$ versus $Group_{AIT2}$ (954.6 ± 248.6 vs. 2,263.6 ± 771, $p < 0.05$), $Group_{Control}$ versus $Group_{ST}$ (954.6 ± 248.6 vs. 2,083.2 ± 987.5, $p < 0.05$), $Group_{Control}$ versus $Group_{GD/TMNG}$ (954.6 ± 248.6 vs. 1,611.6 ± 716.3, $p < 0.05$). Overall, in AIT2, plasma β-G activity is higher than in AIT1 and similar to subacute thyroiditis. Individuals with AIT1 have similar levels of β-G activity with patients with GD/TMNG as well as with controls.

Subsequently, to perform ROC curve analysis, we divided our patients into two groups, based on whether or not their disease involved thyroid tissue destruction: AIT2 and subacute thyroiditis were considered as destructive processes, while AIT1, GD/TMNG, and controls as non-destructive. ROC analysis demonstrated that β-G activity had a high predictive value for destructive conditions (AUC 0.846, 95% CI 0.748–0.943) (Fig. 2). A β-G activity value of 1,480.5 nmol 4-MU/mL plasma/h was identified as the optimal cut-off value to discriminate between destructive and non-destructive thyroid conditions (sensitivity 74%, specificity 82%).

Discussion

To the best of our knowledge, this is the first study to examine the plasma activity of β-G in the setting of AIT. We showed that plasma β-G activity is significantly higher in AIT2 compared to AIT1.

Owing to its high iodine content (37% by weight approximately or 75 mg of iodine per 200 mg tablet) and to its structural resemblance to thyroid hormones, amiodarone is the commonest cause of medication-induced thyroid dysfunction [16]. There are two different mechanisms that can lead to AIT and, hence, two forms of AIT have been described. AIT1 is a Jod-Basedow phenomenon [2], whereas AIT2 is a form of destructive thyroiditis [1, 2]. Notably, there are patients where the two mentioned pathogenic mechanisms co-exist, giving rise to "mixed" forms of AIT [2].

Due to the distinct pathogenic mechanisms of AIT1 and AIT2, the appropriate treatment in each case is different, namely thionamides in AIT1 and steroids in AIT2 [3]. Hence, discriminating between AIT1 and AIT2 is of paramount importance in order to avoid subjecting these patients – who have high risk of developing dangerous tachyarrhythmias – to combined treatments that may be not as effective and incur adverse reactions. However, making the distinction between AIT1 and AIT2 in clinical practice is not always that easy. To the present, a single test or marker that could reliably distinguish AIT1 from AIT2 is not available. Mixed forms of AIT (an overlap between AIT1 and AIT2) also exist, further complicating our decision making. In our study,

only clear-cut cases of AIT1 and AIT2 were included. This was achieved by a strict methodology, requiring the concurrent presence of multiple criteria (ultrasound appearance, CFDS, antibody detection, nuclear imaging) in favor of a subtype in order to assign a patient to it. Suspected mixed forms were excluded from the study. We also retrospectively validated our initial patient classification by assessing the response to treatment: all 9 patients of the AIT1 group who received methimazole and all 9 patients of the AIT2 group who were treated with methylprednisolone achieved euthyroidism without the need of any additional treatment. We can therefore be confident that our patient groups were well designed.

Given the difficulty in differentially diagnosing between AIT1 and AIT2 as well as the serious clinical implications, the search for an easy-to-perform test able to readily identify each AIT subtype is long-standing. Several serum biochemical markers have been tested, but results are of limited value. Pearce et al. [17] showed that levels of serum high-sensitivity CRP did not differ significantly between patients with AIT1 or AIT2 and controls. Bartalena et al. [8] found that IL-6 was markedly elevated in AIT2 but not AIT1 patients. However, their findings were not adequately replicated in subsequent studies, hence questioning the value of IL-6 as a good discriminator [18, 19].

β-G is an acid hydrolase that participates in the breakdown of complex carbohydrates, as well as in the deconjugation of bilirubin and other substances [9, 20]. It is normally located intracellularly in the lysosomes, but during inflammation, it is released in the extracellular fluid. This might be a result of cell membrane dysregulation due to the inflammatory process [13], but it can also stem from secretion by activated neutrophils and eosinophils which accumulate in the inflamed area [10]. In fact, it has been shown that increased activity of β-G in several body fluids is well correlated with bacterial infections [11–13, 21, 22]. β-G is also detectable in the circulation in normal individuals and its plasma activity is positively correlated with age, BMI, and male gender, while genetic polymorphisms of the β-G gene might have a limited influence on the observed inter-individual variation of the enzyme activity [23]. Increased β-G activity has been shown in several circumstances such as liver cirrhosis, acute (e.g., viral hepatitis, pancreatitis) and chronic (rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis) inflammatory diseases [24], and neoplasms [24, 25]. Conversely, in mucopolysaccharidosis type VII, which is caused by β-G deficiency, patients are characterized by a virtually non-detectable plasma activity of β-G [26]. Rare cases of β-G "pseudo-deficiency" (i.e., low in vitro enzyme activity but with no evidence of deficient degradation of natural substrates in vivo) have been described [26]; however, as far as we know, plasma β-G activity has never been formally validated as a diagnostic marker and it is difficult to estimate how the existence of pseudo-deficient individuals might affect its sensitivity or specificity. Finally, although animal studies have shown that exposure to several medications might interfere with β-G activity [27], there is no relevant data in humans. In our study, the subgroups did not differ in regard to age, gender, and BMI. Moreover, none of the participants had a history or clinical signs of the aforementioned conditions known to affect β-G activity.

Our study showed that plasma activity of β-G is markedly increased in AIT2 relative to AIT1. It is noteworthy that in subjects with subacute thyroiditis, which is also a destructive process, there is a rise in β-G activity which is similar to that in AIT2. On the contrary, β-G activity in our patients with AIT1, a process without tissue damage, was similar to that of healthy individuals and that of thyrotoxic subjects with GD/TMNG. The latter had marginally increased β-G activity relative to controls ($p = 0.047$). The presence of patients with GD in this subgroup might be a possible explanation for this finding: GD is characterized by activation of the immune system leading to lymphocytic infiltration of the thyroid gland, and activated inflammatory cells are a possible source of β-G. Lastly, in ROC analysis, β-G activity performed well in distinguishing between destructive and non-destructive thyroid conditions and a cut-off value of 1,480.5 nmol 4-MU/mL plasma/h was able to identify the presence of destructive thyroiditis with a sensitivity of 74% and specificity of 82%.

As our study is preliminary, we chose to assess the performance of β-G activity only in clear-cut cases of AIT1 and AIT2. In mixed forms of AIT, we are in no position to know which of the two processes (destructive or thyroid hyperfunction) prevails and the results might be difficult to interpret.

In conclusion, our study showed that determination of the plasma activity of β-G might be a novel marker with good sensitivity and specificity in discriminating AIT1 from AIT2. Further studies are needed in order to consolidate our findings and also to assess β-G activity in mixed forms of AIT.

Statement of Ethics

The study protocol was approved by the University Hospital of Patras Ethics Committee, while participants gave written informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Georgios K. Markantes: data collection, statistical analysis, manuscript writing. Marina A. Michalaki: study design, manuscript writing. George A. Vagenakis: data collection. Fotini N. Lamari: determination of beta-glucuronidase activity in plasma samples. Efthymia Pitsi: determination of beta-glucuronidase activity in plasma samples. Maria Eliopoulou: study design. Nicholas G. Beratis: study design, manuscript writing. Kostas B. Markou: study design, manuscript writing.

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