The Utilization of an Index for Serum Globulin Compensation in Diseases Associated with Decreased Serum Albumin

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Summary

The albumin globulin ratio (A/G ratio) is meant to represent the ratio of alterations in serum proteins, since, in liver disease, globulins (G) rise following serum albumin (SA) decrease. However, because of the lack of pathophysiological value, its' use has been limited. Alternatively, we have developed an index, the globulin compensation index (GCI) to measure the changes in serum globulins when albumin is decreased. The index is calculated as follows: G – 25 / 35 – SA. The GCI has been tested using retrospective patients' data from the Hospital Universiti Sains Malaysia. Analysis of the data shows that the GCI may be of potential value in showing the actual serum protein status, especially in cases where globulins are decreased along with albumin. Furthermore, globulin rise in cases with reduced albumin was found in 72.3% of cases of hepatic diseases, whereas this finding occurred in up to 32.3% of cases of non-hepatic, systemic diseases.

Key Words: Globulin compensation index, Decreased serum albumin, Serum globular proteins

Introduction

The albumin/globulin (A/G) ratio is a biochemical parameter utilized in the interpretation of changes in serum proteins that accompany disease. The main clinical use of the A/G ratio is when it is reduced as a result of decrease in serum albumin (SA) and the sequential increase in serum globulins (G)[1]. This is the classical change expected to accompany liver disease when SA is decreased below normal levels[1,2]. Its clinical and pathophysiological values have not been clear[3]. Alternatively, measurement of the level of gamma globulins has been suggested, since their increase would be directed against intestinal bacteria, because the liver fails to clear them when they reach the liver through the hepatic circulation[4]. In cases where the decrease in SA is not reciprocated by an increase in G, the A/G ratio, then, does not reflect the real status of change in serum proteins, since it would only be slightly reduced, or not altered at all. Decreased SA levels have been reported in many disease disorders as cancer, kidney diseases, HIV infections, chronic liver diseases, autoimmune diseases, and even in healthy geriatric persons, and have, frequently, been used as markers of deteriorated nutritional status, or markers of unfavourable prognoses [5-8].

In cases of advanced diseases and systemic involvement, globulins may fail to rise in compensation for the hypoalbuminaemia. This work has been set to test a new index, the globulin compensation index (GCI) based on the decreased serum albumin and the globulin levels. The index has been designed to measure the extent of alteration in serum globulins that accompany decreases in serum albumin below normal ranges. In addition to primary hepatic conditions, the

GCI was tested in a variety of non-hepatic systemic disorders, all with reduced serum albumin, and the status of globulin compensation for decreased serum albumin in different diseases condition has been presented and compared to the A/G ratio. The potential clinical usefulness of the GCI has been discussed.

Materials and Methods

The data used in this study was collected retrospectively from the records of the Chemical Pathology Laboratory of the Hospital of the Universiti Sains Malaysia, from a period of 12 months extending from June 2000 until May 2001. The selection criterion was SA below 34 g/L. Names, dates and registration numbers were included. Following the initial selection, each case was followed-up individually through the case sheets at the records office of the hospital. The information sought included age, sex, diagnosis, management, and complications. The data also included laboratory investigations, including liver function tests, total serum proteins (TP), albumin (SA) and/or the A/G ratio.

Because of the wide array of diseases and medical disorders dealt with, exclusion criteria were set. These criteria included patients with recent histories of transfusions of blood and blood components, patients with recent haemorrhages, patients with gammopathies such as multiple myeloma, and patients with protein-losing enteropathies and nephropathies. Hepatic malignancies with systemic involvement were also excluded.

The total number of cases utilized for this study was 333. For study purposes, they were divided initially into a number of groups as follows: 79 cases with malignancies, 26 cases of diabetes mellitus not complicated by nephropathies, 52 cases of chronic infections, 57 cases of neurological disorders, and 43 cases of miscellaneous medical disorders, in addition to 76 cases of hepatic disorders. Ages of patients ranged from 3 to 76 years and the male to female ratio was 1:1.2. The major malignancies were bronchogenic carcinomas, non-Hodgkin lymphoma, pancreatic cancers and colorectal cancers. The major complications in diabetes mellitus patients were septicemia, pneumonia, necrotizing fasciitis, and retinopathies. The most abundant infections were HIV, tuberculosis, meningitis, and bronchopneumonia. Neurological disorders were mostly due to motor vehicle accidents and cerebro-vascular accidents.

Miscellaneous cases included chronic cardiac failure, congenital disorders, allergies and autoimmune diseases. Hepatic disorders included liver cancers, liver cirrhosis, long-standing hepatitis, viral and autoimmune, and cholangitis and cholelithiasis.

The globulin compensation index (GCI) for each patient was calculated using the following equation:

GCI = G – 25 / 35 – SA, where:

GCI is the globulin compensation index, G and SA are the measured concentrations and 25 and 35 represent the minimum of their normal ranges, respectively. Thus, G-25 represents the deviation of G from the lower range of the serum G value, taken as 25 g/L, and 35-SA represents the value of reduction in serum albumin below the minimum of the normal range, taken as 35 g/L (1).

The GCI values obtained were divided into three categories:
1- Negative compensation with negative GCI values (<0.0): all G values were below 25 g/L.
2- Partial compensation, with GCI ranging from 0.0 to < 1.0: all G values were >25 g/L, but the TP values did not rise to 60 g/L.
3- Full compensation, with GCI values >1.0: all G values were > 25 g/L, and the TP values raised to normal ranges, above 60 g/L.

The G levels were calculated by subtracting the values of SA from the value of TP. The baseline value taken for TP was 60 g/L (1). Both the A/G ratio and GCI for each case was calculated individually and plotted in scattering graphs against the relevant globulin concentration (G), where a vertical dotted line represented the GCI value of 1.0. Percentages of cases with compensated and non-compensated TP levels were further calculated and displayed in a histogram. Microsoft Excel was utilized to plot the graphs, and the SPSS was utilized for the statistical analyses. The slope value was calculated using the linear regression analysis formula: y = constant + (slope * x).

Results

The A/G ratios in hepatic diseases showed a reciprocal relationship with G: at low G values, the A/G ratio came to fall within the normal calculated range of 1-2 (Figure 1 a). However, the GCI values for the same cases were found to increase directly as the G values increased (Figure 1 b). In these cases, all GCI values were above 0.0, indicating that they had partial or full

compensation. In systemic diseases, a similar A/G ratio pattern was obtained as that of hepatic diseases, with values falling within normal ranges as G decreased (Figure 2 a). When plotted against their relevant G values, the GCI values for all systemic disorders filled the full range of the three categories, namely, negative, partial and full compensation, with GCI increasing directly with G, as shown by the trendline (Figure 2 b). The values for the slopes were calculated for both hepatic and systemic diseases. With the A/G ratio, the slope values were highly insignificant with both hepatic and systemic diseases (-38.15 and -27.729, respectively). However, the slope values obtained with the GCI were highly significant when used with data from hepatic and non-hepatic, systemic disorders (3.438 and 7.435, respectively). However, the r2 values were more significant with the A/G ratio than the GCI (Figures 1 and 2).

When the data in figure 2 b was split into the individual systemic groups, a similar pattern was obtained, with an increase in GCI as G increased, with negative, partial and full compensation were obtained in each of those disease groups (Figures 3 a to 3 e).
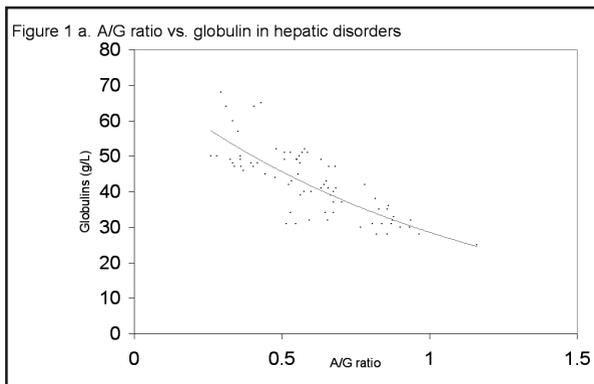
From the GCI values, the percentages of the compensation status in each disease group, including the hepatic group, were calculated (Figure 4): the percentages of negative compensation were 31.6 in the malignancy group, 15.4 in the diabetes mellitus group, 11.5 in the chronic infections group, 17.5 in the neurological disorders group, and 16.3 in the group of miscellaneous medical cases. The average percentage of negative compensation in all the systemic disease group cases was 20.2. In the hepatic group, however, no cases with negative compensation were obtained (Figure 4).
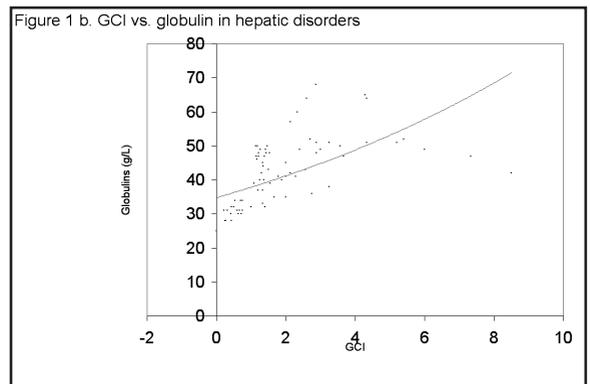
The percentages of cases with partial compensation obtained were 40.6 in the malignancy group, 61.5 in the diabetes mellitus group, 52.0 in the chronic infections group, 47.4 in the neurological disorders group, and 46.5 in the group of miscellaneous medical cases. The average percentage of all the above, non-hepatic cases was 47.4. In the hepatic group, the percentage of partially compensated cases was 27.6 (Figure 4).

The percentages obtained in cases with full compensation were 27.8 in the malignancy group, 23.8 in the diabetes mellitus group, 36.5 in the chronic infections group, 35.1 in the neurological group, and 37.2 in the group of miscellaneous medical cases. The arithmetic average percentage of all above, non-hepatic cases was 32.3. The percentage of fully compensated cases in the hepatic group was 72.4 (Figure 4).

No relations were established between the age and gender of patients with the level of compensation.

Figure 1 a. A/G ratio vs. globulin in hepatic disorders

Figure 1 b. GCI vs. globulin in hepatic disorders

$r^2 = 0.635$, slope = - 38.015, when p is < 0.001.

$r^2 = 0.318$, slope = 3.438, when p is < 0.001.

Fig. 1: The distribution of A/G ratio vs. globulins (Fig 1a) and GCI vs. serum globulins (Fig. 1b) as calculated from data obtained from patients with hepatic disorders with reduced serum albumin.

Figure 2 a. A/G ratio vs. globulin in systemic disorders
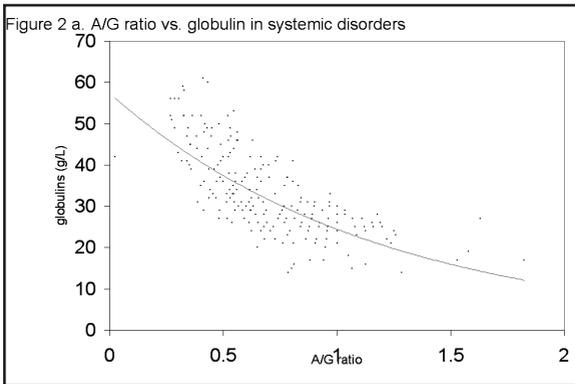
$r^2 = 0.518$, slope = - 27.729, when p is < 0.001.

Figure 2 b. GCI ratio vs. globulin in systemic disorders
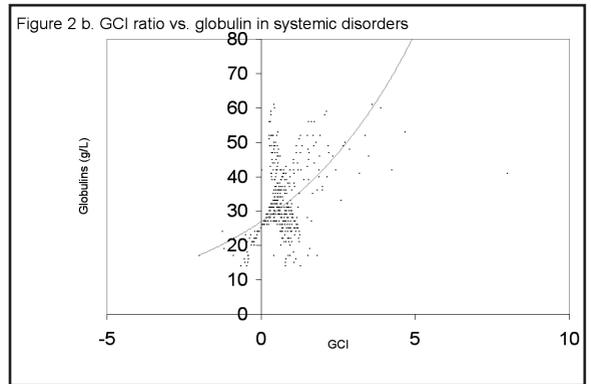
$r^2 = 0.603$, slope = 7.435, when p is < 0.001.

Fig. 2: The distribution of A/G ratio vs. serum globulin. (Fig. 2a) and GCI vs. serum globulin (Fig. 2b) as calculated from of data patients with systemic non-hepatic disorders with reduced serum albumin.

Figure 3 a

Figure 3 b

Figure 3 c

Figure 3 d

Figure 3 e
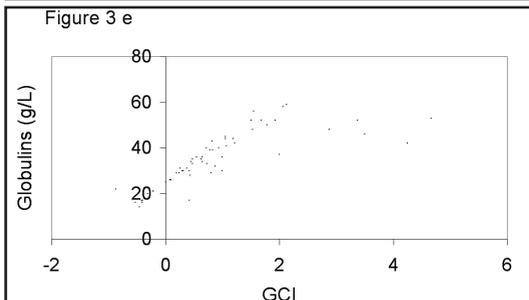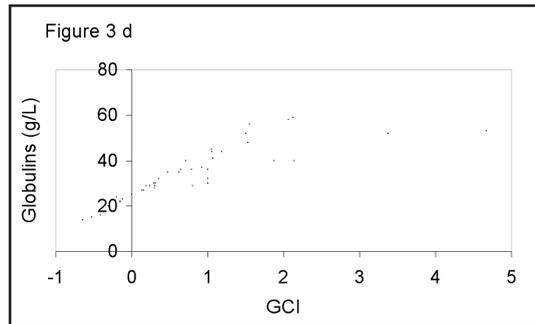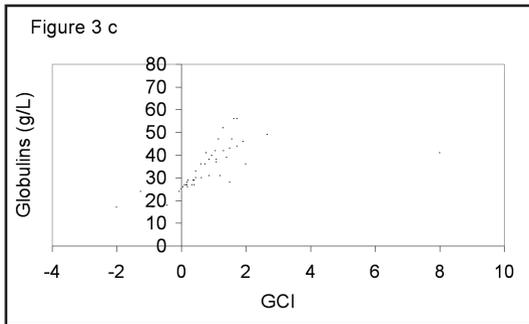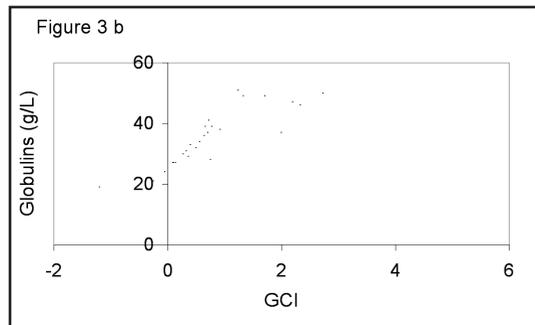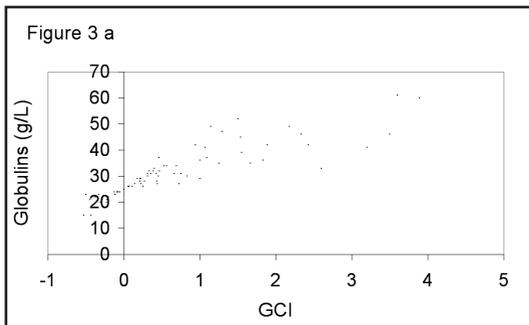
Fig 3 a to 3 e:
The values of GCI obtained from patients with systemic, non-hepatic disorders with reduced albumin plotted against serum globulin. 3a: malignancies, 3b: Diabetes mellitus, 3c: infections, 3d: neurological disorders, 3e: general medical cases.

	malignan-cies	D. mellitus	chronic infections	neurologic	miscella-neous	systemic disorders	hepatic disorders
■ negative compensation	33.6	15.4	11.5	17.5	16.3	21.2	0
□ partial compensation	34.6	61.5	52	47.4	46.5	46.5	27.7
■ full compensation	31.8	23.1	36.5	35.1	37.2	32.3	72.3
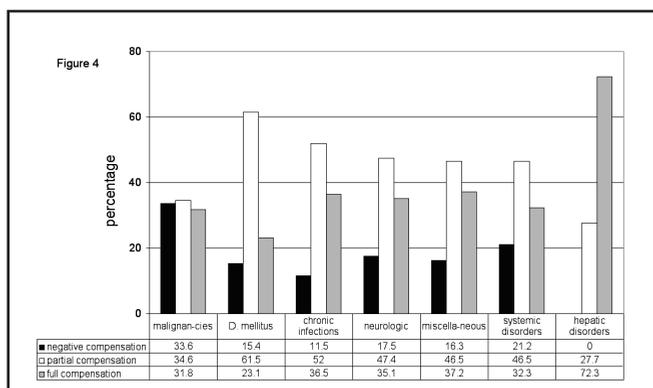
Fig. 4: The percentages of the globulin compensation status among the study cases. The first five on the left of the histogram are the five groups of non-hepatic cases, and the sixth shows the cumulative percentage of all the non-hepatic cases. The extreme right represents the percentages in hepatic cases.

Discussion

Protein synthesis is an inherent property to all body cells. However, there is a clear difference between the different cell types regarding the types and quantities of proteins produced. There are also differences, within the same tissue, in gene expression, following body demands, and availability of the requirements for protein synthesis. Pathologic alterations in the protein synthetic capacity have been reported in disease, which are reflected in the protein content of serum. The liver normally comprises approximately 15% of the total protein synthesizing capacity of the body. The remaining 85% is distributed among other tissues. In cases where tissue protein synthesis is reduced, the liver protein-synthesizing capacity of the liver may rise up to over 30% in compensation[9]. Conversely, once the protein synthetic capacity of the liver is affected, SA levels are reduced, and, this is compensated for by proteins synthesized in extra-hepatic tissues. Thus, a new state of balance is created, widely known as an altered albumin/globulin ratio (A/G) ratio[1].

However, analysis of the data obtained in this work, shows that the A/G ratio is not a consistent marker of serum protein changes: as it was found to be reduced in cases with decreased SA and increased G, the A/G ratio tended to revert to normal as both SA and G were reduced simultaneously.

Moreover, and in spite of the fact that the GCI is applicable only in the presence of SA levels below 35

g/L, the index allows classifying the cases with decreased SA into the three obtained categories of serum proteins being either fully, partially, or negatively compensated. At the time when the A/G ratio tended to lose its' function as a marker for the serum protein changes in such cases when G is reduced simultaneously, the GCI consistently allowed an insight into the state of advancement of disease, which may reflect the severity of the disease, as well as the nutritional status. The lack of consistency in the A/G ratio is most probably the reason for abandoning it. Thus, the GCI may prove to be a good alternative to the A/G ratio, and prove to be useful in the assessment of chronic diseases and the nutritional status. Moreover, it may prove to be useful in the assessment of prognosis in chronic debilitating disorders.

The statistical analyses have shown that the slope values were highly significant for the GCI. This means that GCI changes follow directly the changes in globulin levels. However, the r^2 values of GCI were less significant compared with those of the A/G ratio. This finding is rather expected, due to the wide range of systemic diseases, and the variations in the biological responses. The significant slope values imply that the GCI expresses the actual changes that follow the albumin reduction, at the time when the A/G ratio does not express the changes, especially in cases of reduced globulin.

The implications of this categorization has been further tested in disease states associated with decreased SA where the GCI values were categorized according to type of disease, or organ involvement. In addition, GCI values obtained have allowed the classification of disease states with decreased SA into two categories: those with primary hepatic involvement, with no clinical indications of systemic involvement, and diseases with extra-hepatic origin. This information is not new to clinicians, yet, when presented in this systematic way, it shows that protein compensation in hepatic diseases follows a conventional pattern in 72.3% of cases, with no negative compensation. In systemic diseases, however, the compensation status in terms of globulin increases, and in terms of resumption of normal levels of total serum proteins was found to be positive in only 32.3% of patients.

The principle of serum protein alteration in chronic debilitating diseases is that the extra-hepatic protein-synthesizing capacity is affected in chronic debilitating diseases by a number of mechanisms[9-15]. At the same time, the liver fails, in these cases, to maintain normal SA levels, mainly due to stringency in nutritional requirements, and not due to reduced protein-synthesizing capacity[16-17]. Thus, the presence of reduced SA, that is not accompanied by a significant rise in the level of serum globular proteins, often accompanies, more closely, a state of fatigue or cachexia [10-15]. In cachexia of advanced disease, factors and mechanisms leading to reduced protein synthesis and increased protein catabolism, have been described, in addition to factors leading to cell death and DNA fragmentation. The most extensively described among these factors are tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), lipid mobilizing factor (LMF) and proteolysis inducing factor (PIF)[11-13], [18-20]. These may act singly or together, and the deterioration in the clinical status appears to accelerate close to death, implying that these factors may act in a concentration-related fashion [21].

In conclusion, it may prove that the data presented here may provide guidelines for the assessment of patients with established diagnoses, and the use of the GCI may also be a potentially useful tool in the measurement of protein-synthesizing capacity, in assessing the nutritional status of the body, in evaluating the response of patients to therapy, and in predicting the outcome of disease.

A systematic and prospective study may provide more information regarding the underlying mechanisms involved and the clinical usefulness of GCI.

Acknowledgements

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