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7.6 Reference Intervals for Plasma Proteins in Patients with Non-Insulin Dependent Diabetes Mellitus

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When reference intervals are established based on a healthy reference population they may have limited application for clinical purposes, as the average age of the reference individuals often is different from the age of patients (6). This is especially important for plasma proteins, where concentrations often are changing with age (cf. section 7.2). Furthermore, some chronical diseases can be considered stable (a certain state of health) at another - well defined - level. It is, therefore, important to establish these reference intervals in order to evaluate the results, when other diseases are to be examined.

In some diseases, such as non-insulin dependent diabetes mellitus (type 2 diabetes), there are abnormalities in the metabolism, which is most pronounced for the glucose metabolism. Type 2 diabetes patients are characterized by insulin-resistance in liver and skeletal muscle (1, 2). This insulin resistance is partly compensated by an elevated release of insulin, but the net result is cellular insulin deficiency. Insulin in reduced amounts causes changes in most metabolic processes and might influence the synthesis of plasma proteins.

The object of this investigation was primarily to establish reference intervals for nine selected plasma proteins in patients with non-insulin dependent diabetes mellitus, and secondly to get informations which could evaluate the theory that cellular insulin defiency affects protein synthesis.

Materials

Non-insulin dependent diabetic patients 60 to 80 years of age and without diabetic complications were chosen. They had no concurrent diseases and they were all in a stable metabolic situation treated either with diet alone or with diet and antidiabetic drugs/or insulin, and could be considered in a stable metabolic condition.

Eighty-three patients were primarily included, but 23 of these were later excluded due to missing samples (7), elevated ESR (12), M-component (2), and immediate post study disease (3).

Of the 60 included patients, the HbA_{1c}-concentrations were: mean 9.0 % with range 5.4 to 16.0 %, and ESR: mean 12.3 with range 3 to 28.

Methods

Blood samples were drawn under the same conditions as for the healthy reference samples (cf. section 7.2). Analytical methods were performed on a Cobas Fara (Odense) according to the same instructions and with the Nordic calibrator and with antisera from DAKO.

Results

The results are illustrated as probit-plots and compared to the distributions of concentration values for healthy individuals including the group more than 50 years of age for each plasma protein (cf. section 7.2 and 7.3). Further, the median of the healthy group from 60 to 80 years of age is indicated.

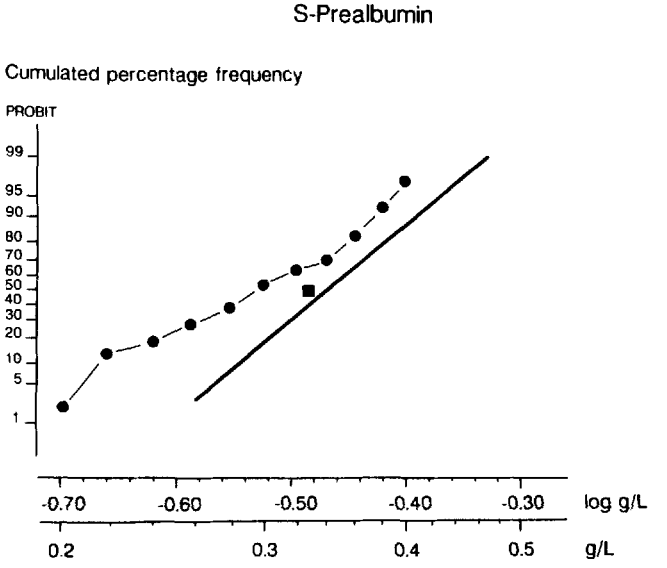

Fig. 7.6.1 *Distribution of S-Prealbumin concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

S-Prealbumin

The distribution of S-Prealbumin is reduced approximately 10 % compared to the healthy reference population (all minus women below the age of 50 not using estrogens) as well as the reference group of the same age group (Fig. 7.6.1). This means that type 2 diabetic patients have about 10 percent lower values compared to the healthy population, and that the reference interval for these should be changed accordingly.

S-Albumin

S-Albumin for the diabetic population is reduced approx. 8 % compared to the reference population (all men and women over 50 years and women below 50 using estrogens) (Fig.7.6.2). Furthermore, the matched reference population of the same age group is not reduced. Consequently, the S-Albumin concentrations are reduced by approximately 8 percent, and the reference interval for type 2 diabetics should be reduced accordingly.

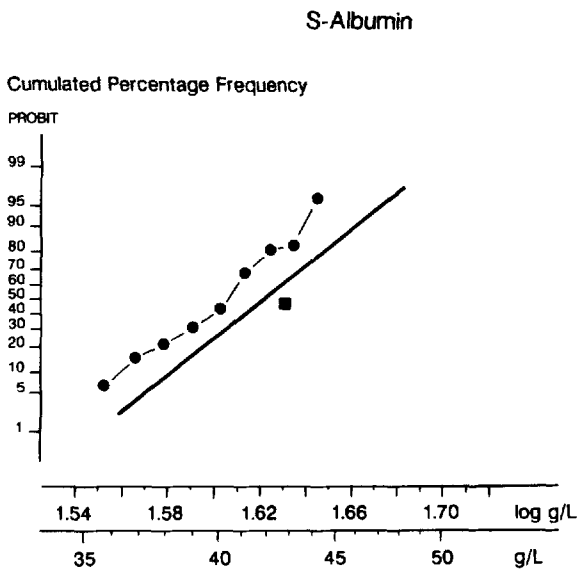

Fig. 7.6.2 *Distribution of S-Albumin concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

S-Orosomucoid

The distribution of S-Orosomucoid concentration values is indistinguishable from the healthy reference population (Fig. 7.6.3), so the reference interval is valid.

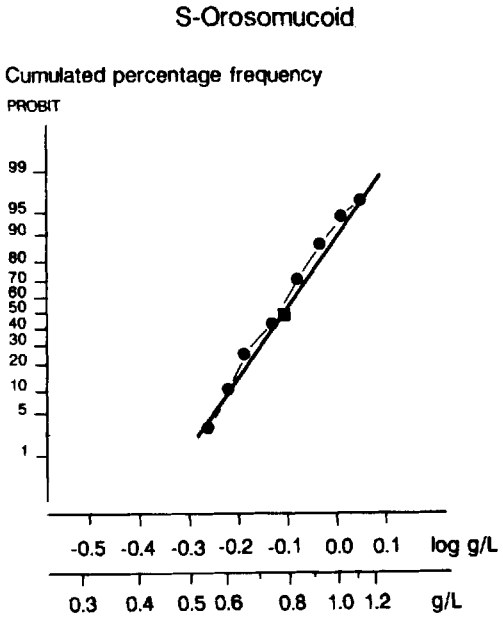

Fig. 7.6.3 *Distribution of S-Orosomucoid concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

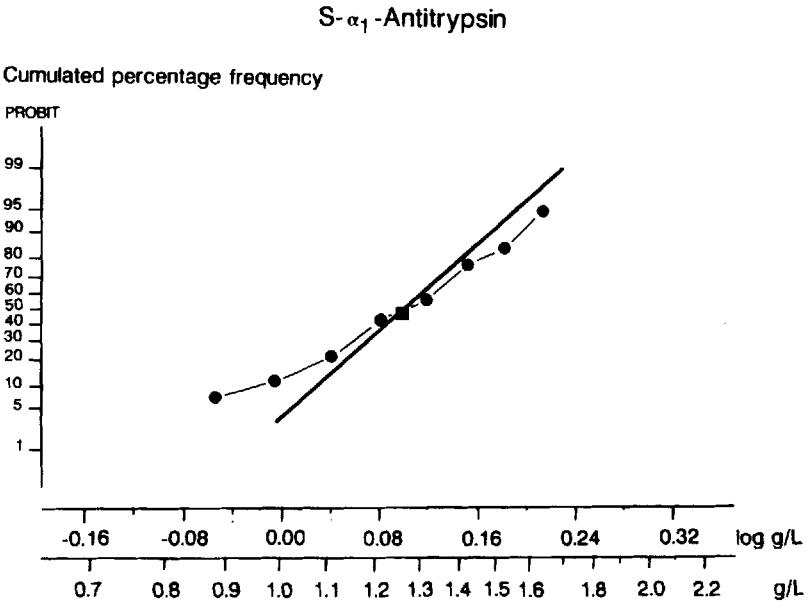

Fig. 7.6.4 *Distribution of S-α_1-Antitrypsin concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

S-α_1-Antitrypsin

S-α_1-Antitrypsin is comparable to the healthy reference population with a slightly broader distribution (Fig. 7.6.4). The type 2 diabetics have not been genotyped, so a fraction of 5 to 10 % of the individuals are expected to belong to MS and MZ types, who have lower concentration values (cf. section 7.3). This might explain the fraction of approximately 10 % of patients with lower values in the distribution. There is, therefore, no need for a separate reference interval for diabetic type 2 patients for this protein.

S-Haptoglobin

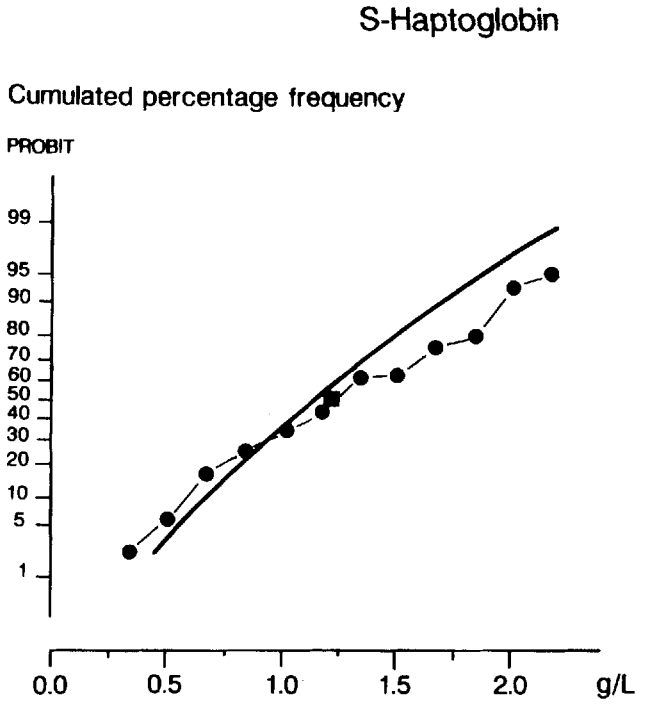

Fig. 7.6.5 *Distribution of S-Haptoglobin concentration values for the diabetic population (•) compared to the healthy reference population (curve). The median of the healthy 60 - 80 age group is indicated (■).*

For S-Haptoglobin, the distribution of values for the healthy reference population is neither Gaussian or log-Gaussian (section 7.2). The distribution for type 2 diabetics, however, seems to be close to Gaussian (Fig. 7.6.5.). Compared to the total reference population over 50 years of age the distribution is broader, but as the median for the matched age-group is indistinguishable we have chosen not to recommend any change in the reference interval for type 2 diabetics.

S-Transferrin

The distribution of S-Transferrin concentration values for type 2 diabetics is approximately 5 % towards lower compared to the healthy reference population consisting of all except from women below 50 years of age (Fig. 7.6.6). The matched age-group, however, has a median close to the median for the diabetics. Therefore, there is no reason for a separate reference interval for this protein.

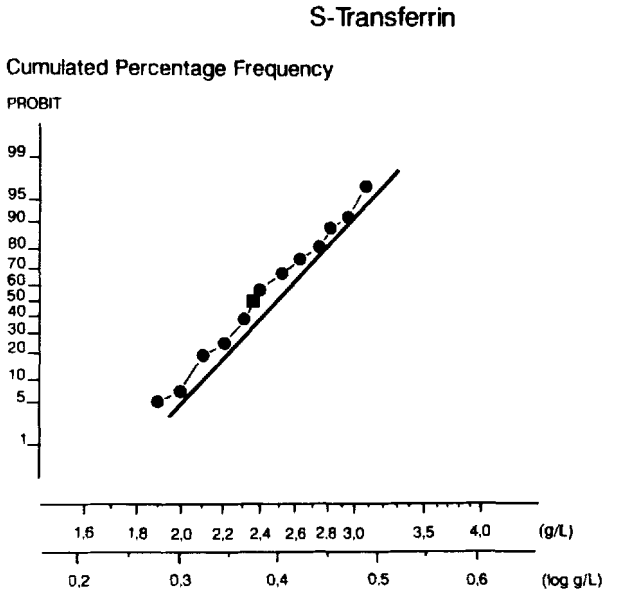

Fig. 7.6.6 *Distribution of S-Transferrin concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

S-IgA

For S-IgA the distributions of two age-groups (one below and one above 50 years of age) are neither Gaussian nor log-Gaussian (cf. section 7.2), whereas the type 2 diabetics seem to have S-IgA-values distributed close to Gaussian (Fig. 7.6.7). This distribution is moved towards higher concentration values, with the matched age group of the healthy population is moved accordingly. Therefore, there is no indications for choosing a separate reference interval for type 2 diabetics for this protein.

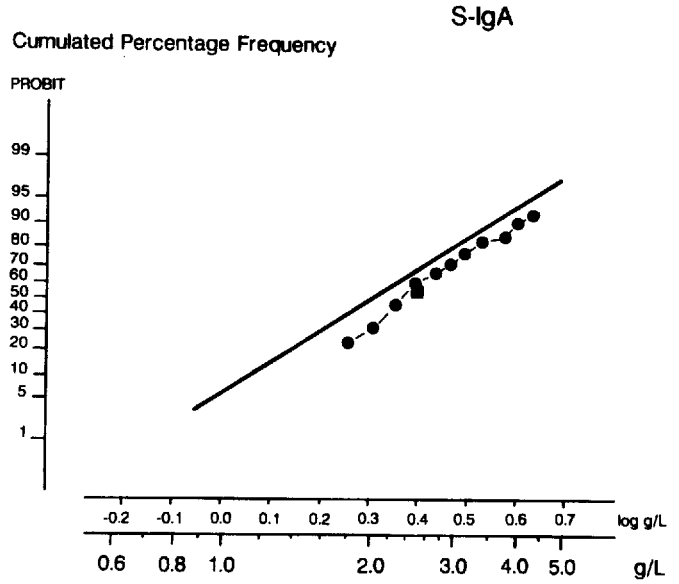

Fig. 7.6.7 *Distribution of S-IgA concentration values for the diabetic population (•) compared to the healthy reference population (curve). The median of the healthy 60 - 80 age group is indicated (■).*

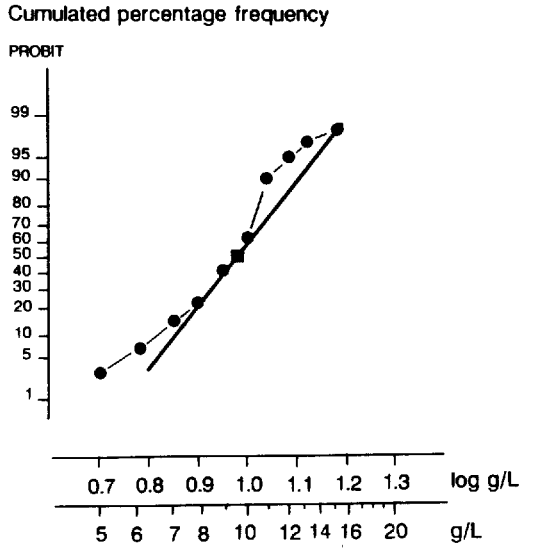

Fig. 7.6.8 *Distribution of S-IgG concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

S-IgG

The distribution of S-IgG concentration values for type 2 diabetics is neither Gaussian nor log-Gaussian but has a median close to the distribution of all healthy individuals minus women below 50 years of age - and also to the age-matched healthy population (Fig. 7.6.8). There is, therefore, no reason for using a separate reference interval for S-IgG for type 2 diabetic patients.

S-IgM

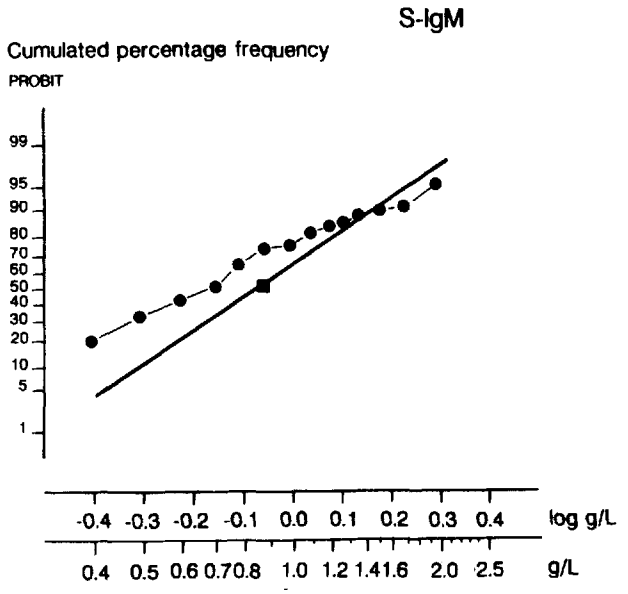

Fig. 7.6.9 *Distribution of S-IgM concentration values for the diabetic population (•) compared to the healthy reference population (straight line). The median of the healthy 60 - 80 age group is indicated (■).*

For S-IgM the distribution of concentration values for the type 2 diabetics is lower than the healthy reference population (all minus women below 50 years of age) and the median is also lower than the age-match reference group (Fig. 7.6.9). This means that the diabetic patients have lower S-IgM-values in general, and in consequence the lower reference limit should be moved to approx. 0.25 g/L.

Discussion

In chronical diseases like type 2 diabetes, the metabolic condition can be considered stable for long periods - but at another metabolic level. This *steady-state* condition may be reflected in the reference intervals, which could be expected to differ from the reference intervals based on healthy individuals.

The consequences of well defined reference intervals for specific diseases, would be a better interpretation of laboratory-data, e.g. could the lower intervals for S-Prealbumin and S-Albumin for type 2 diabetes patients lead to more correct interpretation of low concentration values compared to the general reference intervals. Thus, extended hospitalization or protein supplementation to diabetic patiens (which is without effect) could be avoided. Therefore, the knowledge of these changes may be important for general practitioners and for hospitals in interpretation of protein data.

The model should also be applied to other laboratory analyses and to other chronic diseases which can be considered stable for longer periods of time.

In this study the decrease in S-Prealbumin and S-Albumin, without measurable changes in the other proteins (except from S-IgM, see below) may be explained by a decreased protein synthesis due to cellular insulin deficiency as insulin is acting as an anabolic hormone (3 - 5). Insulin exerts its effect intracellularly in mainly the liver and skeletal muscle, where most of the plasma proteins are produced in the liver. The type 2 diabetic patient is insulin resistant, i.e. decreased effect of insulin in muscle and liver - and compensate by releasing increased amounts of insulin. The increased insulin release, however, does not fully compensate the insulin resistance - with the result of peripheral insulin deficiency. This insulin deficiency leeds to intracellular lack of nutrients to the metabolic pathways (cellhunger) and corresponds to the normal hunger/starvation situation where decreases in Prealbumin, Albumin, and Transferrin are experienced. There is no concomitant increase in the acute phase proteins, which indicates that a situation of cellular hunger due to insulin deficiency, but not to inflammation exists in type 2 diabetes.

The tendency to lower values in this selected patient category for S-IgM is difficult to interpretate.

Conclusions

The reference intervals for S-Prealbumin and S-Albumin are reduced for this selected group of type 2 diabetic patients compared to the general reference intervals for healthy individuals. This could be due to a cellular insulindefiency as there exists an altered metabolic condition in the liver and skeletal muscle, which affects protein synthesis.

Acknowledgements

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