Acta Paediatrica Hungarica, 25 (1–2), pp. 111–117 (1984)

Serum beta$_2$-microglobulin level in type I diabetes: its dependence on the duration of diabetes and the quality of metabolic control

E G Janssen, H U Jastram, K Paschen, B Strobel, M G Bachem

Department of Paediatrics and Central Laboratory, Academic Teaching Hospital, Kaiserslautern, FRG

As the level of serum beta$_2$-microglobulin (β_2-M) has been shown to reflect renal function, its concentration was determined in serum and urine of patients affected by diabetes type I of various duration and quality of metabolic control. 104 diabetic patients, aged 7–39 (mean, 14.8) years, with an average duration of diabetes of 5.7 ± 4.8 years studied as outpatients. Haemoglobin A_1, β_2-M in serum and urine, serum creatinine and protein were determined. The patients were classified into groups according to the quality of control (excellent, satisfactory or poor) and the duration of diabetes (less than 5 years, 5–8 years, more than 8 years). In patients with a duration of less than five years, lower β_2-M levels were found if the quality of metabolic control was good than in patients controlled poorly (1.36 and 1.64 mg/l, respectively). Again in the group with a duration exceeding 8 years, patients with better control had a lower β_2-M level than poorly controlled ones. Diabetics exhibiting a β_2-M level higher than 1.6 mg/l, the upper limit of the normal range, had had diabetes for 8.6 years on the average, while those with a normal serum value only for 3.8 years. These findings have also been confirmed in 47 type I diabetics participating in a holiday camp.

About one third of all patients affected by type I diabetes develop nephropathy in the course of their disease [13]. Most of these patients die with uraemia before their fiftieth year of life [13, 45].

The typical course of diabetic nephropathy is as follows. At the onset of diabetes and during the next few years nephron hypertrophy with a concomitant elevation of the glomerular filtration rate (GFR) occurs [9, 11, 14, 19, 22]. Thickening of the glomerular basal membrane may be observed not earlier than two years after the manifestation of diabetes [32]. This is followed by hyaline atherosclerosis, intracapillary glomerulosclerosis and thickening of the basal membrane of the proximal tubule [28], as reflected by a gradually increasing proteinuria, deterioration of GFR and excretory renal function [28, 41]. The average life-span is seven years from the onset of proteinuria and five years from the elevation of the serum creatinine level [2].

The best tool for judging renal function is measuring the GFR by determining the clearance of various exogenous or endogenous substances. The most reliable method, that of inulin clearance, is quite impracticable in clinical routine. The relia-

bility of the endogenous creatinine clearance is reduced by the fact that creatinine is secreted to some extent also by the tubules. The use of ^{51}Cr-EDTA involves radiation load to the patient and necessitates sophisticated devices [21]. For these reasons, clearance methods carried out in an exact manner are not routinely used for screening and follow-up of renal function. Measuring serum creatinine and the daily protein excretion is a widespread method for this purpose but it only detects a reduction of the GFR below the value of 45 ml/min/1.73 m^2 [41, 44].

Seeking for better diagnostic methods, an endogenous substance was found, the serum level of which showed a much closer correlation to GFR than serum creatinine; it is beta$_2$-microglobulin (β_2-M) [5, 7]. This protein has a molecular weight of 11, 800 and contains 100 amino acids [7, 25, 34, 40]. It is identical with the light chain of HLA-antigens and similar to the CH_3-region of IgG [35] present on the surface of all cells containing a nucleus [16, 17, 37]. The rate of its synthesis is fairly constant, 150–250 mg per day [24, 25, 40]. Breakdown of β_2-M takes place exclusively in the kidney. It is completely filtered by the glomeruli, 99.8 % of the filtered substance is reabsorbed in the proximal tubules and completely catabolized to the level of individual amino acids [7, 25, 34, 40]. Its serum half-time amounts to 40–107 min [12, 24]. The normal urine contains extremely small quantities of β_2-M, its urinary concentration is elevated in tubular damage. There is a close inverse correlation between GFR and the serum β_2-M level [40] which increases with age and its normal value lies between 0.8 and 2.4 mg/l [16, 26]. Its serum level increases in glomerular damage [25, 26, 40, 44, 46] and may be elevated in certain neoplastic disorders accompanied by an increased rate of production of the protein [1, 10, 12, 15, 30, 39, 42, 43], in lymphoid proliferation and inflammatory disorders [6, 18, 25].

There is a close inverse correlation between the serum level of β_2-M and ^{51}Cr-EDTA clearance [26, 44]. A detectable increase of the serum level can be observed in cases with a slight decrease of the GFR below 80 ml/min/1.73 m^2 when the creatinine level is mostly still normal [44]. Serum β_2-M estimation is thus a reliable screening method for early detection of glomerular damage whenever other disorders with elevated serum β_2-M levels can be excluded.

Since there are no published data on serum β_2-M concentrations in patients affected by type I diabetes, still without proteinuria and an elevated serum creatinine level, it seemed promising to compare the serum β_2-M level of such patients with those of age-matched healthy subjects and to investigate whether it was related to the duration of diabetes or the quality of metabolic control.

Materials and Methods

A total of 104 type I diabetes patients attending our diabetes clinic participated in the study; 54 were males and 50 were fe-

TABLE I

HbA_1, creatinine and β_2 M levels in 104 diabetic patients and 47 control subjects, means and standard deviations

	HbA_1 per cent	Creatinine mg/dl	β_2–M mg/l
Diabetics n = 104	10.8±1.8	0.77±0.18	1.48±0.58
Controls n = 47	6.8±0.6	0.74±0.14	1.39±0.27

males, their mean age was 14.8 (range, 7 to 39 years). The mean duration of diabetes was 5.7 years with a span from 0.5 to 26 years. Patients with acute or chronic inflammatory disease, proteinuria, arterial hypertension, neuropathy or retinopathy were excluded from the study. All patients received conventional insulin therapy twice daily and a caloric oriented diet with a fixed carbohydrate content. All patients had completed a course in metabolic control, diet and adjusted insulin treatment of diabetes. An age-matched group comprising 47 healthy subjects having no metabolic disorders, renal disease, inflammatory processes or tumour served as the control group.

In addition to the usual parameters of diabetes care the following data were determined

1. β_2-M, measured by the Phadebas-β_2-microglobulin test, provided by Pharmacia Diagnostics for Germany, Deutsche Pharmacia GmbH, Freiburg

2. Creatinine, by a modified Jaffé-reaction.

3. HbA_1, after separation by column chromatography on an Isolab microcolumn, provided by Panchem GmbH, Kleinwallstadt, FRG.

For statistical analysis, means and standard deviations and correlation coefficients were calculated and Student's t test and the Wilcoxon test were applied.

RESULTS

The routine quality control performed daily yielded the following values of variation coefficients: β_2-M: 5.6%, creatinine: 2.1%, HbA_1: 3.4%.

The means and standard deviations are shown in Table I.

The 95% fiducial limits for normal serum β_2-M were, 0.88 and 1.92 mg/l.

The distribution of β_2-M concentration in diabetics and the controls is compared in Fig. 1. Although the mean values (1.48 and 1.39 mg/l) hardly differed, diabetics exhibited a wider scatter. Among the latter 18% had a level exceeding the normal limit (1.9 mg/l), 5% had a level lower than 0.8 mg/l. The lowest value found in the control group was 0.86. There was no difference in this respect between male and female patients.

Figure 2 illustrates the relationship between duration of diabetes and serum β_2-M. Patients having diabetes for more than 12 years exhibited a higher mean level than those with a duration shorter than 12 years. The percentage of patients with an elevated β_2-M level increased with the duration of diabetes. The correlation between serum β_2-M and duration of diabetes was rather close, r being 0.58 ($p < 0.001$).

The influence of metabolic control on serum β_2-M is shown in Fig. 3. Patients with good metabolic control

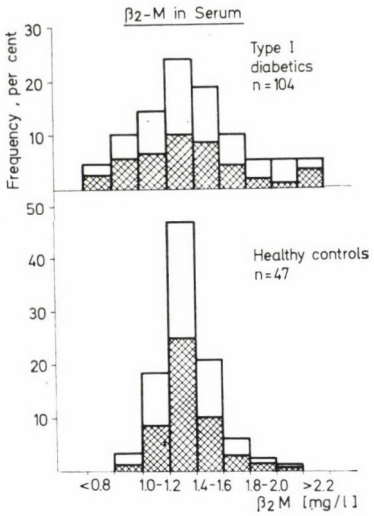

FIG. 1. Serum beta$_2$-microglobulin level in type 1 diabetics and healthy controls. Upper part of columns show male, the lower part female, subjects

and a duration exceeding 8 years had β_2-M levels not differing from those of patients with good control but a duration of less than five years (1.38 and 1.36 mg/l, respectively). Both groups with poor metabolic quality exhibited significantly higher, sometimes pathological values ($p < 0.01$).

DISCUSSION

According to several authors [4, 8, 26, 40, 41, 46], serum β_2-M is a reliable measure of GFR as long as conditions accompanied by increased synthesis of this protein can be excluded. The fact that in a fraction of patients low

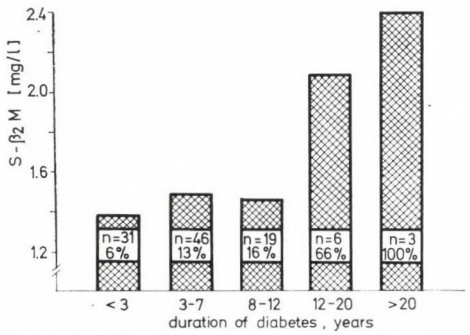

FIG. 2. Mean serum beta$_2$-microglobulin level in type 1 diabetics with disease of various duration. The number of patients (n) and the percent frequency of pathological values is shown in the columns

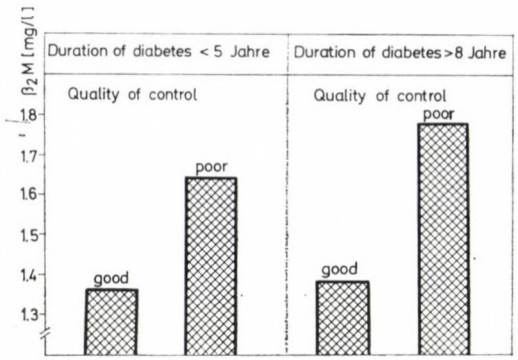

FIG. 3. Serum beta$_2$-microglobulin level and the quality of metabolic control in diabetes of shorter and longer duration. Concentrations below 10% correspond to a good metabolic control, and those above 12% to a poor metabolic control

levels of serum β_2-M were found is in full agreement with the observation of increased GFR values during the first few years of diabetes [9, 11, 14, 19, 22]. The factor determining the increased GFR is of haemodynamic nature, acting by altering renal flow and leading thus to changes in the effective filtration pressure [23]. This is morphologically reflected in nephron hypertrophy [19], in an increase of the mean glomerular volume [31] and of the capillary surface [20], and in an expansion of the kidney volume detectable by sonography [11].

The question why this stage is followed by diabetic nephropathy resulting in kidney failure in about 30% of patients and why the majority of diabetics never pass beyond the stage of microalbuminuria has not yet been answered.

Of the diabetics participating in this study, 18% had a high β_2-M level after a few years. This points to a narrowing of the glomerular function in the presence of normal serum creatinine and absence of proteinuria, in agreement with the observations of several authors [26, 44] who showed that a reduction of GFR and elevation of the serum β_2-M level may occur in the so-called creatinine-blind stage. Further, they have demonstrated a closer relationship between β_2-M and GFR than between serum creatinine or creatinine clearance and GFR.

Although there was a significant positive correlation between duration of diabetes and serum β_2-M in general, patients with poor metabolic control had an elevated mean serum value independently of the duration of their diabetes. It would follow that the quality of control is a more powerful factor in the course of diabetic nephropathy than the duration of diabetes. This is in full agreement with the findings obtained by Pirart [36] in a retrospective study and by Schlienger et al [41]. We are performing a prospective study to see whether the reversibility or slowing down of morphological and functional renal changes by good metabolic control of diabetes

observed in animal experiments [27, 38] were valid for human patients. Vigorous antihypertensive therapy applied in patients affected by manifest nephropathy accompanied by arterial hypertension may slow down the progression of nephropathy [29] or reduce the rate of renal proteinloss [33].

Our findings together with data in the literature on β_2-M concentration in patients with type I diabetes, may turn out to be helpful in early recognition, control and prognosis of diabetic nephropathy and in planning a reasonable treatment.

References

1. Amlot PL, Adinolfi M: Serum β_2 microglobulin and its prognostic value in lymphoma. Eur J Cancer 15:791, 1978
2. Andersen AR, Andersen JK, Christiansen JS, Deckert T: Prognosis for juvenile diabetics with nephropathy and failing renal function. Acta Med Scand 203:131, 1978
3. Bachem MG: Auswirkungen der Einstellungsqualität auf das HbA_1, den Lipid- und Elektrolytstoffwechsel bei Typ I Diabetes mellitus. Inauguraldissertation, Universität Bonn 1981
4. Bailey RR, Tisch GW, Pearson S: Serum β_2 microglobulin in the assessment of renal function. NZ Med J 87: 607, 1979
5. Berggard I, Bearn AG: Isolation and properties of a low molecular weight β_2-globulin occurring in human biological fluids. J Biol Chem 243:4095, 1968
6. Beorgchia S, Vincent C, Revillard JP, Trepo C: Elevation of serum β_2 microglobulin in liver diseases. Clin Chim Acta 109:245, 1981
7. Bernier GM: β_2 microglobulin: structure, function and significance. Vox Sang 38:323, 1980
8. Braren V, Goddard J, Brill AB, Touja JJ: Beta-2-microglobulin as a renal diagnostic agent. Urology 13:624, 1979
9. Brenner BM, Hostetter TH, Olson JL, Rennke HG, Venkatchalam MA: The role of glomerular hyperfiltration in the initiation and progression of diabetic nephropathy. Acta Endocrinol (Copenh) 97: Suppl 242, 7, 1981
10. Child JA, Spati B, Illingworth S, Barnard D, Corbett S, Simmons AV, Stone J, Worthy TS, Cooper EH: Serum beta 2 microglobulin and C-reactive protein in the monitoring of lymphomas. Cancer 45:318, 1980
11. Christiansen JS, Frandsen M, Svendsen PA, Gammelgaard J, Parving HH: Rapid changes in kidney function-factors influencing kidney function in diabetics and normal men. Acta Endocrinol (Copenh) 97:Suppl 242, 11, 1981
12. Cooper EH, Plesner T: Beta-2-microglobulin review: its relevance in clinical oncology. Med Pediatr Oncol 8:323, 1980
13. Deckert T, Andersen AR, Christiansen JS, Andersen JK: Course of diabetic nephrology. Factors related to development. Acta Endocrinol (Copenh) 97: Suppl 242, 14, 1981
14. Ditzel J, Junker K: Abnormal glomerular filtration rate, renal plasma flow and renal protein excretion in recent and short-term diabetics. Br Med J 1:13, 1972
15. Ellegaard J, Morgensen CE, Kragballe K: Serum beta$_2$-microglobulin in acute and chronic leukaemia. Scand J Haematol 25:275, 1980
16. Evrin PE, Wibell L: The serum levels and urinary exretion of β_2-microglobulin in apparently healthy subjects. Scand J Clin Lab Invest 29:69, 1972
17. Grey HM, Kobo RT, Colon SM, Poulik MD, Cresswell P, Springer T, Turner M, Strominger JL: The small subunit of HL—A antigens in β_2-microglobulin. J Exp Med 138: 1608, 1973
18. Grützner FJ: Diagnostik mit β_2-Mikroglobulin. Inn Med 9:45, 1982
19. Gundersen HJG, Gotzshe O, Hirose K, Kroustrup JP, Morgensen CE, Seyer-Hansen K, Osterby R: Early structural changes in glomerular capillaries and their relationship to long-term diabetic nephropathy. Acta Endocrinol (Copenh) 97:Suppl 242, 19, 1981
20. Hirose K, Tsuchida H, Osterby R, Gundersen HJG: A strong correlation between glomerular filtration rate and filtration surface in diabetic kidney hyperfunction. Lab Invest 43:434, 1980
21. Hör G, Heidenrich P: Nierendiagnostik in der Nuklearmedizin. Schnetzer-Verlag, Konstanz 1980, p. 109
22. Hostetter TH, Troy JL, Brenner BM: Glomerular hemodynamics in experi-

mental diabetes mellitus. Kidney Int 19:410, 1981
23. Jensen PK, Christiansen JS, Steven K, Parvin HH: Renal function in diabetic rats. Acta Endocrinol (Copenh) 97:Suppl 242, 25, 1981
24. Karlsson FA, Sege K, Beauduin M, Pluygers E, Wibell L; Groth T, Peterson PA: Turnover studies of β_2 microglobulin in normal persons and in patients with increased serum levels of protein. Phadedoc No 3, Uppsala: Pharmacia Diagnostics AB 31, 1978
25. Karlsson FA, Wibell L, Evrin PE: β_2-microglobulin in clinical medicine. Scand J Clin Lab Invest 40:27, 1980
26. Kult J, Lämmlein C, Röckel A, Heidland A: β_2-Mikroglobulin im Serum, ein Parameter des Glomerulumfiltrats. Dtsch Med Wochenschr 99:1686, 1974
27. Maurer SM, Brown DM, Steffes MW: Studies on the reversibility of kidney changes in experimental diabetes in the rat. Acta Endocrinol (Copenh) 97: Suppl 242, 29, 1981
28. McMillan D: Renal vascular changes in diabetes and their predicted effects. Acta Endocrinol (Copenh) 97:Suppl 242, 26, 1981
29. Morgensen CE: Long-term antihypertensive treatment (over six years) inhibiting the progression of diabetic nephropathy. Acta Endocrinol (Copenh) 97:Suppl 242, 1981
30. Norfolk D, Child JA, Cooper EH, Kerruish S, Millford Ward A: Serum β_2-microglobulin in myelomatosis: potential value in stratification and monitoring. Br J Cancer 42:510, 1980
31. Osterby R, Gunderson HJG: Glomerular size and structure in diabetes mellitus. I. Early abnormalities. Diabetologia 11:225, 1975
32. Osterby R, Gotzsche O, Gunderson HJG, Hirose K, Lundbaek K, Seyer-Hansen K: Progression of glomerular structural kidney alterations in diabetic rat and man. Acta Endocrinol (Copenh) 97:Suppl 242, 63, 1981
33. Parving HH, Andersen AR, Smidt U, Frisberg B, Bonnevie-Nielsen V, Svendsen PA: The natural course of glomerular filtration rate and arterial blood pressure in diabetic nephropathy and the effect of antihypertensive treatment. Acta Endocrinol (Copenh) 97:Suppl 242, 39, 1981
34. Peterson, Evrin PE, Berggard I: Differentiation of glomerular, tubular and normal proteinuria. Determinations of urinary excretion of β_2-microglobulin, albumin, and total protein. J Clin Invest 48:1189, 1969
35. Peterson PA, Cunningham BA, Berggard I, Edelman GM: Beta$_2$-microglobulin — a free immunoglobulin domain. Proc Natl Acad Sci USA 69:1697, 1972
36. Pirart J: Glycaemic control and development of diabetic neprhopathy. Acta Endocrinol (Copenh) 97:Suppl 242-41, 1981
37. Poulik MD, Bernoco M, Bernoco D, Ceppelin R: Aggregation of HL—A antigens at the lymphocyte surface induced by antiserum to β_2-microglobulin. Science 182:1352, 1973
38. Rasch R: Studies on the prevention of glomerulopathy in diabetic rats. Acta Endocrinol (Copenh) 97:Suppl 242, 43, 1981
39. Rashid SA, Copper EH, Axon ATR, Eaves G: Serum $\beta_2$microglobulin in malignant and benign diseases of the stomach and pancreas. Biomedicine 33:113, 1980
40. Revillard JP: La β_2 microglobuline: structure, fonction et métabolisme. Lyon Méd 241:681, 1979
41. Schlienger JL, Reiss D, Anceau A, Simon C, Stephan F: La béta-2-microglobuline. Intérêt en diabétologie. Sem Hôp Paris 58:959, 1982
42. Shuster J., Gold P, Poulik MD: β_2-microglobulin levels in cancerous and other disease states. Clin Chim Acta 67:307, 1976
43. Späti B, Child JA, Kerruish SM, Cooper EH: Behaviour of serum β_2-microglobulin and acute phase reactant proteins in chronic lymphocytic leukaemia. Acta Haematol (Basel) 64:79, 1980
44. Viberti GC, Keen H, Mackintosh D: Beta$_2$-microglobulinaemia: a sensitive index of diminishing renal function in diabetics. Br Med J 2:95, 1981
45. Watkins PJ: Predicting determination in renal function. Acta Endocrinol (Copenh) 97:Suppl 242, 55, 1981
46. Wibell, L, Evrin PE, Berggård I: β_2-microglobulin in renal disease. Nephron 10:320, 1973

Received 4 May 1983

Prof E G Janssen
Städtisches Krankenhaus
6750 Kaiserslautern, GFR