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Different frequencies of diabetic complications in insulin-treated patients with diabetes of comparable duration, in relation to age at onset of diabetes

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The prognosis and quality of life of diabetic patients are primarily determined by the development of such diabetic complications as retinopathy, nephropathy, neuropathy, cardiovascular diseases and amputations[1,7,8]. Very important in this context are diabetic retinopathy, the most frequent diabetic complication, and nephropathy. The latter leads to the proportionally greatest mortality in insulin-dependent diabetics, accounting for more than 50% of all deaths in diabetics younger than 40 years of age[14]. The frequency of complications is usually described by rates of incidence and prevalence. For diabetic retinopathy there are two different incidence rates: one for non-proliferative retinopathy, which is characterized by a cumulative risk of about 90%, 15 years after onset of diabetes, and another for proliferative retinopathy, which is the main cause of blindness, with an abrupt increase between 10 and 15 years of diabetes duration. The cumulative risk shows a constant rise up to 60% within 40 years of the onset of diabetes[2–5]. The incidence rate of diabetic nephropathy increases during the first 15 years of diabetes duration and then decreases. The cumulative risk is 35% after a diabetes duration of 40 years[11]. Considering these results, and the fact that with increasing age the duration of diabetes increases too, the age at onset of diabetes is a relevant factor in the development of diabetic complications. This prompted us to investigate the frequencies of diabetic retinopathy and nephropathy in insulin-treated diabetics in relation to the age at diabetes onset.

According to clinical experience diabetes onset in puberty, which may be associated with an increased risk of developing these complications, is assumed to play a role in this context. Therefore we test the following hypothesis:

"Onset of diabetes in infancy and youth, including puberty, and at an adult age, may be associated with different risks of developing diabetic complications in insulin-treated diabetics."

Patients and methods

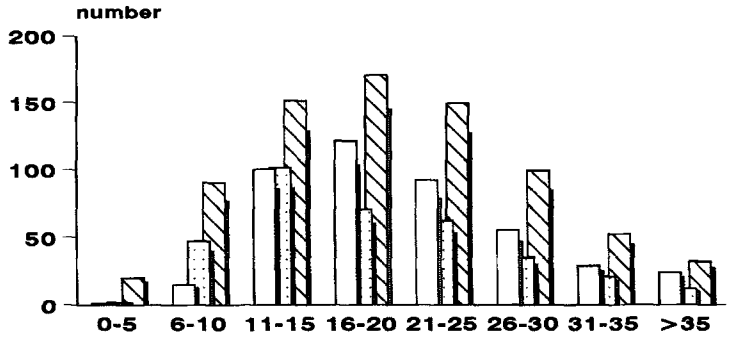
Only a few investigations have been performed with large groups of patients. Therefore in our investigation we included all insulin-treated diabetics with hospitalization periods in our institute from 1980 to 1989. The patients came from the five new Federal States (area of the former GDR) of the FRG. Because our institute was a centre of diabetes care, we primarily had to do with patients who had great problems in their metabolic control and/or suffered from diabetic complications. Most of them were treated in our hospitals up to the final stage of the disease. The data we present in this report are therefore the data from a specialized centre of diabetes care. So far no study has been performed concerning the factors involved in referral to our hospital. However, neither patients from urban nor those from rural regions were overrepresented and no other special selection was made. Furthermore, in patients with diabetes onset before the age of 15 a selection bias could be excluded, because about 70% of all known diabetics were hospitalized once or twice-yearly in our clinic.

On the basis of the National Diabetes Register of the former GDR, rates of incidence and prevalence of insulin-treated diabetes have been described previously[13]. The prevalence of insulin-treated diabetes in people under the age of 30 years increased from $97/10^5$ in 1980 to $117/10^5$ in 1989.

Our hypothesis was tested by a retrospective study using the data of 5276 hospitalizations between 1980 and 1989. All patients were insulin-treated, and the age at onset of diabetes was under 30 years. Although all patients were classified as having type I (insulin-dependent) diabetes according to criteria of the World Health Organization[12], misclassification cannot be excluded. In particular, some of the patients with diabetes onset after an age of 15 years may be not classical type I diabetics, but on the other hand we have previously reported a good agreement of incidence and prevalence rates of insulin-treated diabetics within the first 30 years of age on the basis of the National Diabetes Register.

Assessment of alterations in the eyes was based on an ophthalmological examination. The status of retinopathy was classified as non-proliferative or proliferative retinopathy as described before[15]. The stratification according to the age at onset of diabetes was fixed empirically considering the fact that most patients with a diabetes onset between the ages of 10 and 15 years were in puberty. This was assessed by the Tanner stage of pubic hair and breast or genital development. More than 80% of

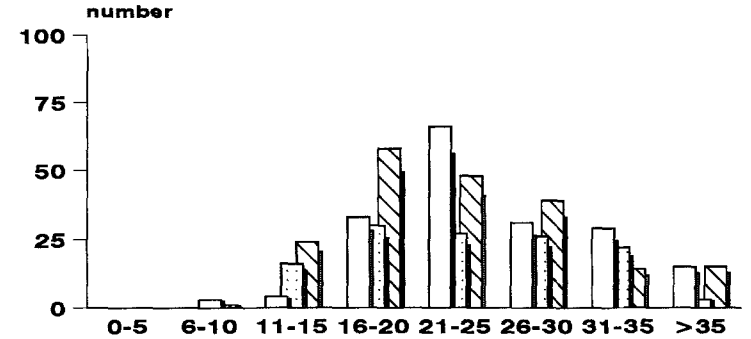
Non-proliferative retinopathy



	0-5	6-10	11-15	16-20	21-25	26-30	31-35	>35
0-10 years	1	15	100	121	92	55	29	24
11-15 years	2	47	101	70	62	35	21	12
16-30 years	20	90	151	170	149	99	52	32

duration of diabetes

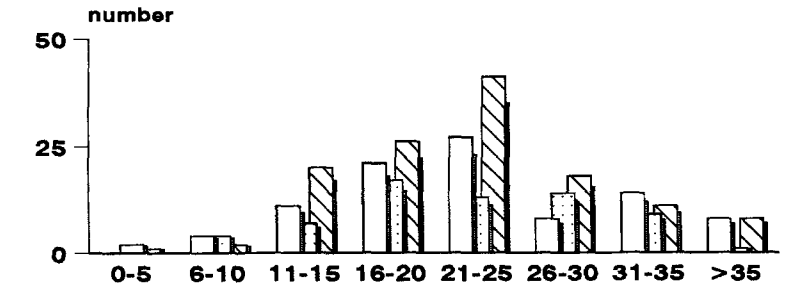
Proliferative retinopathy



	0-5	6-10	11-15	16-20	21-25	26-30	31-35	>35
0-10 years	0	0	4	33	66	31	29	15
11-15 years	0	3	16	30	27	26	22	3
16-30 years	0	1	24	58	48	39	14	15

duration of diabetes

Nephropathy



	0-5	6-10	11-15	16-20	21-25	26-30	31-35	>35
0-10 years	0	4	11	21	27	8	14	8
11-15 years	2	4	7	17	13	14	9	1
16-30 years	1	2	20	26	41	18	11	8

duration of diabetes

Fig. 1. Frequency distributions of retinopathy (non-proliferative and proliferative) and nephropathy on the basis of 5276 diabetics with hospitalizations from 1980 to 1989 in dependence on the age at onset of diabetes.

the patients who developed diabetes between 10 and 15 years of age shared Tanner stages 3 or 4 on the 5-point classification.

Frequency distributions of retinopathy and nephropathy were calculated, and means of diabetes duration were assessed and checked for significant differences between 3 groups, stratified by age at diabetes onset, by Student's t-test. Frequencies were compared on the basis of the Chi^2-test in dependence on diabetes duration, and contingency coefficients were calculated for significantly different frequencies.

The results are presented as dependence on diabetes duration in 5-year intervals. We used the following stratification for the 3 groups, based on the age at diabetes onset:

group 1 (n = 1776) – onset of diabetes up to the age of 10 years,
group 2 (n = 1285) – onset of diabetes between the ages of 11 and 15 years and
group 3 (n = 2215) – onset of diabetes at an age of 16 to 30 years.

Results

Frequency distributions are given in Figure 1 for retinopathy and nephropathy. As can be clearly seen, the frequencies are normally distributed and no substantial bias exists. The peaks of non-proliferative as well as proliferative retinopathy and nephropathy appear after the same diabetes duration as was found by Klein et al. [2] and Krolewski et al. [4,11]. For comparison of the frequencies in dependence on diabetes duration we had to assume that there are only non-significant differences of the means of diabetes duration between the 3 groups. Means of diabetes duration and the result of the significance tests are given in Table 1. The mean diabetes durations of group 2 and 3 are a little lower (significant, $p \leqq 0.05$) than that of group 1 in patients with proliferative retinopathy. In patients with non-proliferative retinopathy we found signifi-

Tab. 1. Means of diabetes duration according to the stratification used for age at diabetes onset.

	Age at diabetes onset (years)		
	0–10	11–15	16–30
Non-proliferative retinopathy	21.2±7.9 (437)	18.7±7.9 (350)	19.7±8.5 (763)
	└──p≦0.01──┘		
	└──p≦0.01──────┘		
Proliferative retinopathy	25.9±7.3 (178)	23.3±6.9 (127)	23.2±7.1 (199)
	└──p≦0.01──┘		
	└──p≦0.01──────┘		
Nephropathy	23.5±8.0 (93)	21.9±7.6 (67)	22.7±7.5 (127)

Tab. 2. Chi^2-values and contingency coefficients (CC) for comparison of the three groups (according to the age at onset of diabetes) for retinopathy and nephropathy in dependence on diabetes duration.

Diabetes duration		0–5	6–10	11–15	16–20	21–25	26–30
Non-proliferative retinopathy							
Group 1 vs. 2	Chi^2	0.25	23.7[a]	34.9[a]	2.17	3.5	0.0
	CC		0.26	0.35			
Group 1 vs. 3		–	55.9[a]	35.9[a]	9.3[a]	8.8[a]	1.9
			0.37	0.32	0.19	0.20	
Group 2 vs. 3		–	7.2[a]	0.3	0.9	0.26	1.4
			0.14				
Proliferative retinopathy							
Group 1 vs. 2	Chi^2	–	3.5	18.9[a]	7.2[a]	2.2	1.6
	CC			0.26	0.2		
Group 1 vs. 3		–	0.9	19.2[a]	5.6[b]	10.9[a]	0.87
				0.24	0.15	0.22	
Group 2 vs. 3		–	1.5	0.03	0.5	1.4	4.8[b]
							0.19
Nephropathy							
Group 1 vs. 2	Chi^2	5.4[b]	5.0[b]	0.2	2.04	1.06	7.0[a]
	CC	0.17	0.14				0.28
Group 1 vs. 3		1.62	0.77	8.1[a]	0.12	0.74	1.18
				0.17			
Group 2 vs. 3		5.3[b]	8.7[a]	4.3[b]	1.45	0.67	4.0[b]
		0.12	0.16	0.14			0.18

[a] significance ($p \leqq 0.01$)
[b] significance ($p \leqq 0.05$)

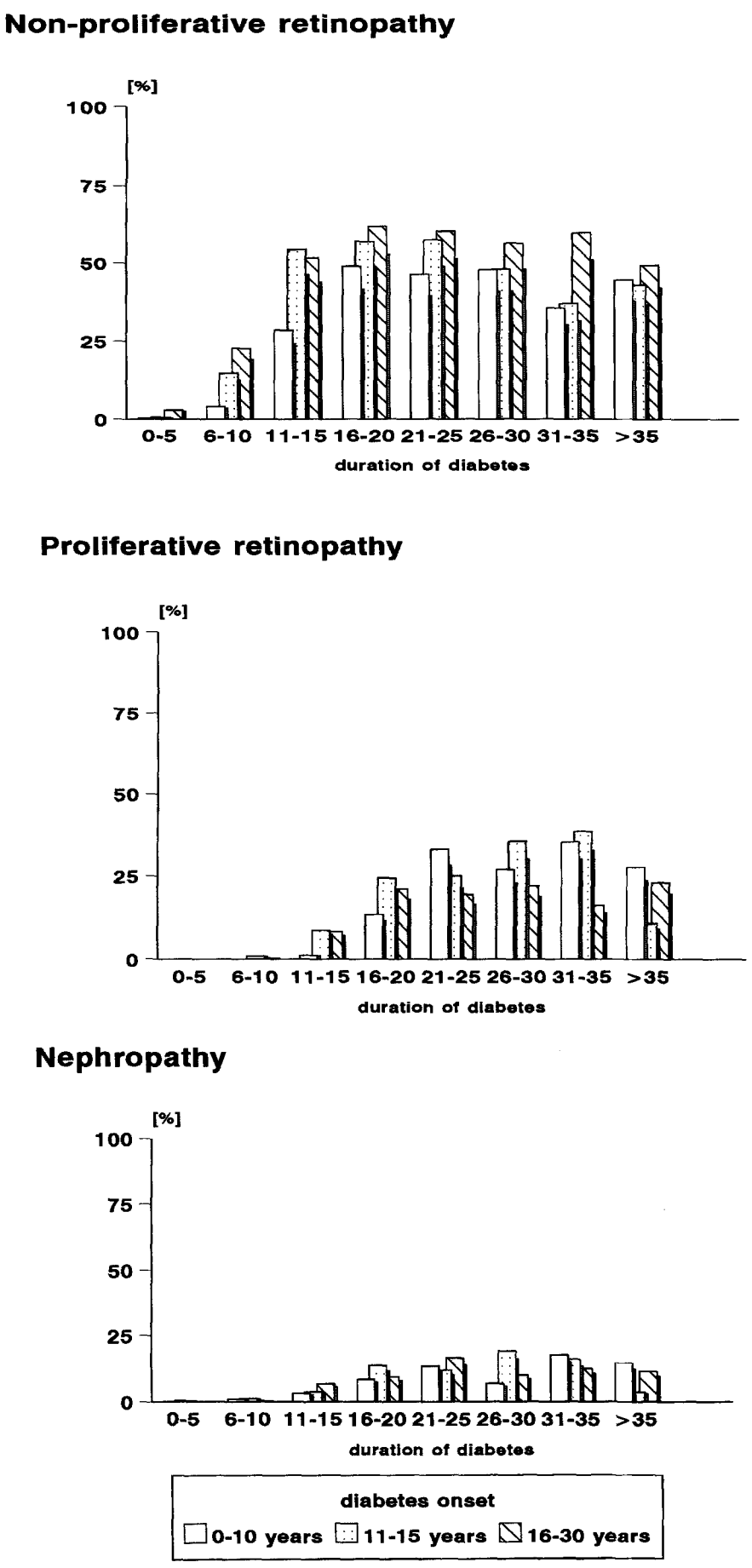


Fig. 2. Risks of insulin treated diabetics to develop retinopathy (non-proliferative and proliferative) or nephropathy in dependence on the age at onset of diabetes.

cant differences between groups 1 and 2 ($p \leqq 0.01$) as well as groups 1 and 3 ($p \leqq 0.05$). Already these tests suggest an increased risk for groups 2 and 3, taking into consideration the higher frequency of non-proliferative and proliferative retinopathy in relation to a significantly lower diabetes duration. On the basis of Table 1 we could calculate the Chi^2-values for comparison of the frequencies of diabetic complications in the three groups.

Table 2 demonstrates the results for retinopathy and nephropathy in dependence on the diabetes duration. Whereas between groups 2 and 3 no differences, or only less significant differences were found, highly significant differences were observed between groups 1 and 2 as well as between groups 1 and 3. This was confirmed by calculation of the contingency coefficient. From the values of the contingency coefficients we could establish a tendency to correlation in all cases. Significant differences occurred only if patients had had diabetes for a period between 5 and 25 years. Whereas in groups 1 and 2 there are only one and two cases of non-proliferative retinopathy within the first 5 years (less than 0.5%), among diabetics with an age at diabetes onset between 16 and 30 years, 3% exhibited non-proliferative retinopathic changes. As demonstrated by the calculated risk, non-proliferative as well as proliferative retinopathy occurred about 5 years earlier in groups 2 and 3 (Figure 2). The risk of non-proliferative retinopathy shows a marked increase between 10 and 15 years of diabetes duration, and proliferative retinopathy developed after a delay of 15 to 20 years. After 20 years of diabetes almost 100% of the patients showed microangiopathic alterations of the retina.

For nephropathy this trend is much weaker and not, or only weakly, significant. After a diabetes duration of 20 years the frequency was similar for all three groups with 13.6%, 12% and 11.8%. A delayed or earlier occurrence of nephropathy, as seen for retinopathy, was not observed.

Discussion

The results of the study confirmed our hypothesis that there are different risks of developing diabetic complications within the three groups, compiled on the basis of age at diabetes onset. The frequency distribution proves that the significant differences between prepubertal and pubertal, or prepubertal and postpubertal diabetes onset (earlier and more frequent appearance of retinopathy in groups 2 and 3) disappear with increasing diabetes duration.

There are no differences between diabetes onset during and after puberty except for a few cases of slight significance (non-proliferative retinopathy with diabetes duration of 6 to 10 years, proliferative retinopathy with diabetes duration of 26 to 30 years, and nephropathy within the first 15 years). A striking phenomenon is that:

a) the groups do not differ significantly after 20 to 25 years of diabetes,
b) group 2 showed a markedly increased risk of these complications up to 20 years after onset of diabetes if compared with group 1,
c) there were no, or only weakly significant, differences between groups 2 and 3.

The suspected relationship of diabetes onset in puberty to an increased risk for an earlier development of diabetic complications could only be confirmed for groups 1 and 2. It seems that patients with diabetes onset before puberty are protected for some time against diabetic complications, but after about 20 years of diabetes duration there are no major differences between them and the other groups. On the other hand, the risk of developing diabetic complications is similar in patients with diabetes onset during and after puberty. Of course, more data concerning metabolic control, heredity and other known risk factors should be taken into account to detect possible causes for the differences observed. But our results do suggest that if diabetes becomes manifest during and after puberty, the disease should be under strict control from the beginning, since strict metabolic control is known to prevent or delay the development of diabetic complications. Our findings definitely emphasize the important role played by early ophthalmological diagnosis, especially in patients with diabetes onset during and after puberty. Further studies should be carried out to find out the causes of the delayed development of diabetic complications in patients with diabetic onset in the prepubertal phase. It may be that the rapid changes of hormonal status which occur in puberty are responsible for this delay; this assumption is supported by the comparable risks of the postpubertal group.

Summary

Diabetic complications such as retinopathy and nephropathy affect the quality of life of diabetic patients. The aim of this study was to find out whether there are differences in the development of these complications associated with the age at onset of diabetes and the different effects of diabetes onset before, during or after puberty. Therefore, we tested the hypothesis whether onset of insulin dependent diabetes in puberty was connected with an increased risk of developing diabetic microangiopathy. We found a significantly increased risk in patients with diabetes onset in puberty up to a diabetes duration of 20 years if compared with diabetes onset before but not with that after puberty. It seems that diabetes onset before puberty delays the development of early diabetic complications and that

changes of the hormonal status during puberty may be responsible for an earlier development of retinopathy. After about 20 years of diabetes there are no significant differences between the groups. Our results emphasize the necessity of early ophthalmological diagnosis and adequate metabolic control, especially in patients with diabetes onset during or after puberty, in order to prevent or delay the development of diabetic complications.

Résumé

La fréquence des complications tardives du diabète chez les patients traités à l'insuline ayant une même durée de diabète, dépend de l'âge du patient lors du diagnostic de la maladie

Les complications tardives du diabète telles que la rétinopathie et la néphropathie compromettent davantage la qualité de vie des diabétiques. Le but de notre étude était de considérer l'âge du patient lors du diagnostic de la maladie (avant, pendant ou après la puberté) comme étant un élément déterminant possible pour le développement des complications tardives du diabète. Les résultats montrent un facteur de risque plus élevé chez les patients atteints pendant ou après la puberté. Il semblerait qu'un diabète apparaissant avant la puberté et traité à l'insuline soit associé à un développement tardif de ces complications, surtout sous forme de rétinopathie. Après vingt ans de diabète, il n'y a plus de différence significative parmi les groupes de diabétiques. Ces résultats soulignent la nécessité d'un diagnostic précoce et d'un contrôle du métabolisme sévère, en particulier chez les patients qui, pendant ou après la puberté, développent un diabète qui nécessite un traitement à l'insuline. Les causes possibles du retardement observé devraient être étudiées dans une clinique spécialisée.

Zusammenfassung

Unterschiedliche Häufigkeit diabetischer Spätkomplikationen bei insulinbehandelten Patienten mit vergleichbarer Diabetesdauer in Abhängigkeit vom Diabetesmanifestationsalter

Diabetische Spätkomplikationen wie Retinopathie und Nephropathie beeinträchtigen in starkem Maße die Lebensqualität von Diabetikern. Ziel unserer retrospektiven Studie war es, das Alter bei Diabetesmanifestation (vor, während und nach der Pubertät) als mögliche Determinante für die Entwicklung diabetischer Spätkomplikationen zu untersuchen. Die Ergebnisse zeigen ein signifikant erhöhtes Risiko von während und nach der Pubertät manifestierten Patienten im Vergleich zur Gruppe vor der Pubertät manifestierter Diabetiker. Es scheint, daß ein vor der Pubertät manifest gewordener insulinbehandelter Diabetes mit einer verzögerten Entwicklung diabetischer Spätkomplikationen, insbesondere der Retinopathieformen, assoziiert ist. Nach etwa 20jähriger Diabetesdauer finden sich keine signifikanten Unterschiede mehr zwischen den Manifestationsaltersgruppen. Diese Resultate unterstreichen die Notwendigkeit frühzeitiger ophthalmologischer Diagnostik und einer strikten Stoffwechselführung insbesondere bei Patienten, die während oder nach der Pubertätsphase einen insulinabhängigen Diabetes entwickeln. Mögliche Ursachen für die beobachtete Verzögerung sollten in entsprechenden klinischen Studien untersucht werden.

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