GLYCATED HAEMOGLOBIN

AS A SURROGATE MARKER FOR THE APPEARANCE AND PROGRESSION OF RETINOPATHY IN TYPE 1 DIABETES MELLITUS

SYSTEMATIC REVIEW AND META-ANALYSIS

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*A study conducted by **HTA Consulting** **www.hta.pl***

Summary

Aims: We performed a systematic review and meta-analysis to examine the association between HbA1c and the appearance and progression of diabetic retinopathy (DR) in T1DM.

Materials and methods: The two electronic medical databases (MEDLINE, CENTRAL) were searched to identify all papers reporting HbA1c level and retinopathy in T1DM. Observational and randomized, controlled trials (RCTs) with at least 1 year of follow-up were included. Estimates were made of the adjusted relative risk (RR) of complications for an increase in HbA1c of 1%. If available data were insufficient to calculate RR, the odds ratio (OR) was estimated. Weighted mean differences (WMD) in HbA1c level between the case group (i.e. with DR) and the control group (i.e. without DR) were also calculated.

Results: We identified 16 trials (4176 patients) that fulfilled the inclusion criteria. Based on four RCTs (n=1597), pooled RR for progression of DR was calculated as 1.24 (95%CI:1.01–1.52) for an increase in HbA1c of 1%. Pooled data from four observational studies (n=910) showed that RR of the incidence of DR was 1.59 (CI:1.34–1.89) for HbA1c increase of 1%. A meta-analysis of eight observational studies (n=1171) demonstrated a lower HbA1c level in patients without DR compared with patients with DR (WMD=0.82 [CI:0.69–0.96]). In addition, a meta-analysis of five observational studies revealed that mean HbA1c values were significantly lower in the group without progression of DR relative to the group with DR (WMD=1.05 [CI:0.37–1.72]). One RCT included data on visual deterioration and macular oedema; analysis demonstrated that an increase in HbA1c level of 1% increased the risk of both macular oedema (RR=1.81 [CI:1.17–2.81]) and visual deterioration (OR=2.2 [CI:1.2–3.9]).

Conclusion: The results of our systematic review indicate a strong correlation between HbA1c level and appearance and progression of DR in T1DM. Thus, HbA1c may be considered an excellent surrogate endpoint for DR in T1DM.

Introduction

- Glycated haemoglobin (HbA1c) is commonly employed in clinical trials as a surrogate marker of diabetes control and the risk of diabetic complications in type 1 diabetes mellitus (T1DM). The efficacy of many glucose-controlling agents has been characterised with respect to HbA1c, without their effects on clinically important endpoints being demonstrated.
- To date, several trials have examined the relationship between the HbA1c level and microvascular complications in T1DM, but no systematic review has been published.
- The aim of our study was to perform a systematic review and meta-analysis of observational studies (OS) and randomized controlled trials (RCTs) to examine the association between HbA1c and the appearance and progression of diabetic retinopathy (DR) in T1DM.

Methods

Relevant articles were identified by means of a systematic literature search conducted in two electronic medical databases (MEDLINE and The Cochrane Library) to identify all papers reporting HbA1c level and DR. A very sensitive search strategy was applied, using more than 100 terms grouped in 3 categories: population (i.e. diabetes mellitus, IDDM, etc), surrogate (i.e. glycated haemoglobin, HbA1c) and clinically important outcome (i.e. retinopathy). The date of the last search was June 2007.

Observational studies and randomized controlled trials (RCTs) that reported HbA1c level in T1DM patients were included. Estimates were made of the adjusted relative risk (RR) of complications for an increase in HbA1c by 1 percentage point (pp). Where necessary, results of the included trials were converted accordingly. The parameter thus calculated reflects how many times the risk increases with the HbA1c level increasing by 1 pp. If available data were not sufficient to calculate the RR, the odds ratio (OR) was estimated instead. Weighted mean differences (WMD) in the HbA1c level (mean value during the observation period) between the case group (i.e. with DR) and the control group (i.e. without DR) were also calculated.

Table 1. Inclusion criteria of the systematic review

	Inclusion criteria	Exclusion criteria
Population	Type 1 diabetes mellitus.	Other types of diabetes
Intervention	Diet intervention or lifestyle modification, oral antidiabetic medications, insulin therapy (conventional, intensive, continuous subcutaneous insulin infusion).	experimental therapies
Methodology	RCTs or observational studies	cross-sectional studies
Observation period	≥ 1 year	None
Clinically important endpoint	Retinopathy defined as: • lesions identified by means of dilated fundus examination, fundus photography or fluorescein angiography, or • visual acuity disturbances due to DR, or • blindness due to DR, or • macular disorders due to DR.	• visual acuity disturbances or blindness due to causes other than DR or imprecisely defined • a history of vitrectomy • evaluation of progression or regression of the lesions following ophthalmic surgery • results expressed as the number of eyes involved and not the number of patients with DR
Surrogate endpoint	Changes in the HbA1c level defined as: • glycated haemoglobin level expressed as the level of the HbA1c fraction; • the level of glycated haemoglobin other than the HbA1c fraction (HbA1 or total glycated haemoglobin) if a method (e.g. formulation) making it possible to convert the reported values into the HbA1c level was provided in the publication; • glycated haemoglobin as measured by means of the HPLC method, ion-exchange chromatography or another method allowing for comparison of the results according to standards assumed in the DCCT study • Data available in the form of: ◦ at least two HbA1c measurements (baseline and at the end of the follow-up period) making it possible to calculate the change in the HbA1c level during follow-up, or ◦ the mean change in the HbA1c level during the study, or ◦ the mean HbA1c level during the study.	None

Conclusions

- The results of RCTs indicate a statistically significant correlation between increasing HbA1c level and rising risk of progression of DR, progression from non-proliferative to proliferative DR, or deterioration of visual acuity.
- The results of observational studies also indicate a statistically significant correlation between increasing HbA1c level and rising risk of DR in T1DM.
- The results of observational study showed that the HbA1c level was higher in patients with DR than in patients without DR.

Our systematic review indicate a strong correlation between the HbA1c level and occurrence and progression of DR in T1DM. Thus, the level of HbA1c may be considered an excellent surrogate endpoint for DR in T1DM.

Results

We identified 16 trials that fulfilled the inclusion criteria, involving a total of 4,176 patients.

Results from randomized controlled trials

Based on four RCTs (n=1597), pooled RR for progression of DR was calculated as 1.24 (95%CI: 1.01-1.52; p=0.039) for an increase in HbA1c of 1%. This correlation was statistically significant (Fig. 1).

In one study it was shown that an increase in the HbA1c level by 1 pp was associated with an increased HR for progression of DR from non-proliferative to proliferative (HR=1.49 [95%CI: 1.14; 1.96])

One RCT included data on visual deterioration and macular oedema; the analysis demonstrated that an increase in the HbA1c level by 1 pp increased the risk of both macular oedema (RR=1.81 [95%CI: 1.17–2.81]; p=0.008) and visual deterioration (OR=2.2 [95%CI: 1.2–3.9]; p=0.001).

Results from observational studies

Pooled data from four observational studies (n=910) showed that RR of the incidence of DR was 1.59 (95%CI: 1.34–1.89; p<0.0001) for an increase in the HbA1c level by 1 pp (Fig. 2).

Meta-analysis of the results of eight observational studies (Fig. 3) indicated that the weighted mean difference in the HbA1c level in the group of patients with DR was higher than that in the group without DR (WMD = 0.82 [95%CI: 0.69; 0.96]).

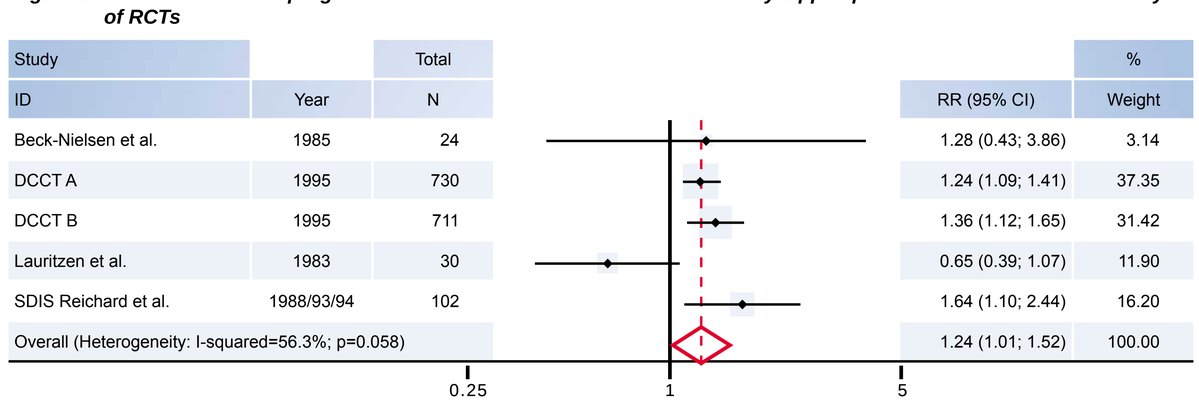
Meta-analysis of the results of the five observational studies (Fig. 4) indicated that the weighted mean difference in the HbA1c level in the group of patients with progression of DR was higher than that in the group without progression of DR (WMD= 1.05 [95%CI [0.37; 1.72]).

Table 2. Summary of the results concerning the relationship between the HbA1c level and DR in T1DM

Endpoint	Number of studies	Number of patients	Study design	Parameter	Parameter value [CI95%]
DR progression	3	156	RCT	RR	1.10 [0.55. 2.19]
	4[a] (5)[b]	1.597		RR	1.24 [1.01; 1.52]
	5	1.415	OS	WMD	1.05 [0.37; 1.72]
Progression from non-proliferative to proliferative DR	1	352	RCT	HR	1.69 [1.42; 2.02]
	1	363		HR	1.49 [1.14; 1.96]
Occurrence of DR	4	910	OS	RR	1.59 [1.34; 1.89]
	8	1.171		WMD	0.82 [0.69; 0.96]
Visual acuity deterioration due to DR	1	102	RCT	OR	2.2 [1.2; 3.9]
Macular oedema (with concomitant proliferative DR)	1	91[c] (102)[d]	RCT	RR	1.81 [1.17; 2.81]

a) the number of studies included in meta-analysis; b) the number of independent results pooled in meta-analysis; c) the number, for which the parameter value was calculated; d) the number of patients enrolled; Values of the RR, OR and HR were converted to reflect an increase in the HbA1c level by 1 pp.

Figure 1. Relative risk of DR progression with an increase in the HbA1c level by 1 pp in patients with T1DM – meta-analysis of RCTs



NOTE: Weights are from random effects analysis

Figure 2. Relative risk of DR occurrence with an increase in the HbA1c level by 1 pp in patients with T1DM – meta-analysis of observational studies

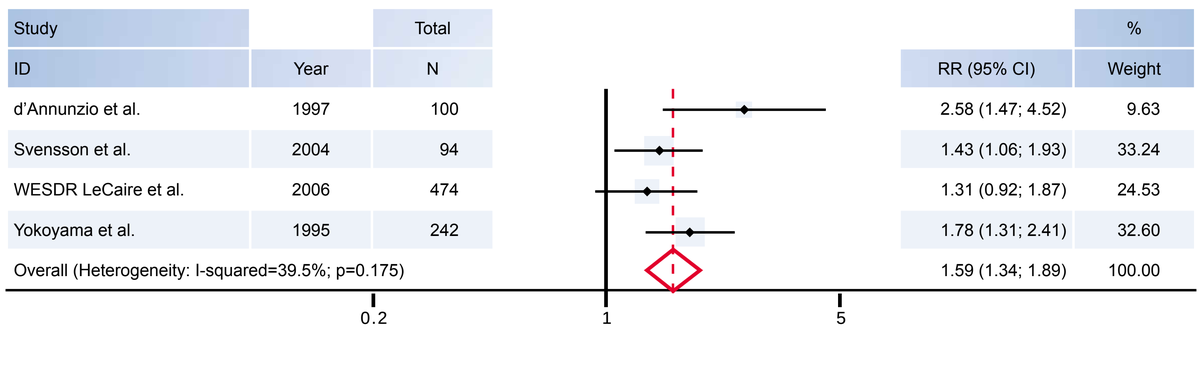
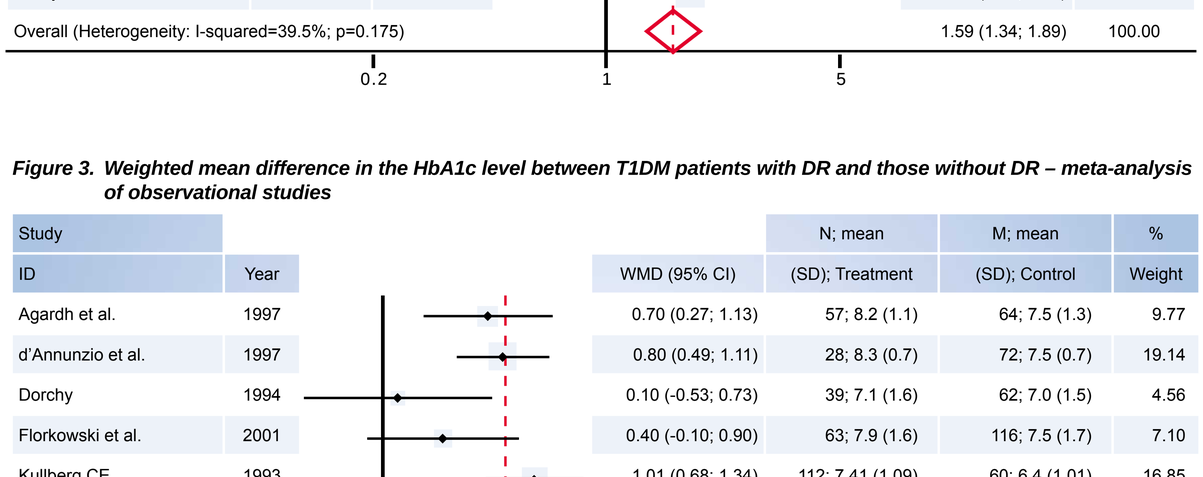


Figure 3. Weighted mean difference in the HbA1c level between T1DM patients with DR and those without DR – meta-analysis of observational studies

Figure 4. Weighted mean difference in the HbA1c level between T1DM patients with progression of DR and those without progression of DR – meta-analysis of observational studies.



NOTE: Weights are from random effects analysis