Relationship between heart rate variability, low grade inflammation and glycated hemoglobin. A sugary sweet story

R. Hadad, S.F. Akobe, P. Weber, S.B. Haugaard, A. Sajadieh

Bispebjerg University Hospital, Copenhagen, Denmark
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Background: Low grade inflammation (LGI) is significantly associated with microvascular complications in diabetes mellitus (DM). Reduced and impaired Heart rate variability (HRV) is a strong marker of autonomic dysfunction and neuropathy and strongly associated with microvascular disease in DM. New studies and observations indicate that the diabetic neuropathic process starts early during pre-diabetes. On the other hand, HRV and LGI are closely interrelated. Our aim was to evaluate whether LGI or hyperglycemia (i.e. high HbA1c) is associated with the autonomic dysfunction or reduced HRV among people with diabetes and pre-diabetes.

Methods and materials: This study is based on The Copenhagen Holter Study, in which 678 community dwelling subjects aged 55 – 75 years who were free of previous cardiovascular disease, except from well controlled hypertension, and who underwent a 48-hours Holter recording. Analysis of HRV including night-time HRV were available for 653 participants and this population included 133 people with well-controlled and newly recognized T2DM (mean HbA1c 55 mmol/mol (7.2%)) and 386 people with pre-diabetes defined as HbA1c between 39 mmol/mol (5.7%) and 47 mmol/mol (6.4%). We selected high-sensitive CRP, as markers of LGI. As measures of HRV we used the standard deviation of normal-to-normal (N-N) beats (SDNN), the root mean square of N-N beats (RMSSD) which has been acknowledged to be best linked to vagal parasympathetic tone, and the mean time between N-N complexes (meanNN) which represents the average 24-hour heart rate (60.000/meanNN = average 24-hour HR in beats/min)

Results: Measures of HRV were associated with HgbA1c among both people with T2DM and pre-diabetes. Among people with pre-diabetes HbA1c was inversely associated with 24-hour RMSSD (r=–0.11, p=0.03) and night-time SDNN (r=–0,13, p>0.01), while among T2DM HgbA1c was only associated with 24-hour RMSSD (r=–0.21, p=0.02). These association stayed significant when adjusted for sex, age, BMI, smoking, HOMA-ir, hs-CRP and systolic blood pressure in multiple linear regression (Table 1). LGI was only associated with HRV in diabetes. HbA1c was not associated with any measures of HRV or LGI among people with normal glucose metabolism.

Conclusion: HRV is closely and inversely associated with HbA1c in both diabetes and prediabetes, but only in diabetes LGI is associated with HRV. This indicates that the process of autonomic dysfunction/neuropathy starts at an early phase during pre-diabetes and probably provoked by postprandial hyperglycemia, while in diabetes both HbA1c and LGI are associated with HRV showing that LGI is activated later in the disease process probably provoked by long-term postprandial hyperglycemia, indicating treatment of hyperglycemia and postprandial hyperglycemia in the prediabetes state may be helpful.

Table 1: Multiple linear regression. Effect of HbA1c and LGI on HRV among people with normal glucose metabolism, pre-diabetes, and diabetes.

Variables of HRV		Normal glucose metabolism	Pre-diabetes	Diabetes
24-hour SDNN	HgbA1c [1]	55	-49	-28
	CRP[2]	-7	-3.3	-12*
Night-time SDNN	HgbA1c[1]	45	-66*	-13
	CRP[2]	-2.7	0.21	2.7
24-hour RMSSD	HgbA1c[1]	0.20	-1.4*	-7*
	CRP[2]	-0.02	-0.02	0.1
Night-time RMSSD	HgbA1c[1]	0.65	-1.40	-0.29
	CRP[2]	0.1	-0.03	0.1
24-hour meanNN	HgbA1c[1]	24	-88	-88
	CRP[2]	-6	-36*	-36**
Night-time meanNN	HgbA1c[1]	142	-156	-129
	CRP[2]	-18	-31*	-53**

Results are presented as slope (p-value).

**P-value <0.05*

***P-value <0.01*

[1]Adjusted for sex, age, BMI, smoking, HOMA-ir, hs-CRP and SBT.

[2]Adjusted for sex, age, BMI, smoking, HOMA-ir, HgbA1c and SBT.

Logarithmic values of RMSSD, HgbA1c and CRP is used, as these are not normally distributed.