

Serum bilirubin levels and risk of prediabetes in young and healthy adults

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PURPOSE

- Inflammation and oxidative stress have been implicated in the development of diabetes mellitus.
- The antioxidant and anti-inflammatory effects of bilirubin have been increasingly recognized.
- Biomarkers associated with early changes in glucose homeostasis may help to improve diabetes risk prediction in the general population.
- Our aim was to assess the relationship between bilirubin levels and risk of prediabetes in young and healthy individuals.

METHODS

- We performed a population based cross-sectional study of 1758 healthy individuals aged 25-41 years which were enrolled in the population based 'Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors' (GAPP) Study in the Principality of Liechtenstein.
- Exclusion criteria: 1.) Known diabetes; 2.) BMI >35kg/m²; 3.) Prevalent cardiovascular disease.
- Serum bilirubin and glycosylated hemoglobin (HbA_{1c}) were assayed from fasting venous blood samples using a Cobas 6000 (Roche, Switzerland) and high-performance liquid chromatography (Bio-Rad D-10, Switzerland).
- Prediabetes was defined as HbA_{1c} between 5.7-6.4%.
- Multivariable linear and logistic regression models were adjusted for sex, age, BMI, smoking status, lipid profile, glomerular filtration rate (GFR), HbA_{1c}, uric acid, high sensitivity CRP and transaminases.

Table 1 Baseline characteristics

Total n = 1758	Normoglycemia n = 1322	Prediabetes n = 436	p-Value
Male sex (%)	599 (45.3)	237 (54.4)	0.001
Age (y)	37 (32; 40)	39 (34; 41)	<0.0001
BMI (kg/m ²)	24.4 3.7	25.4 3.8	<0.0001
Curr. smoking (%)	252 (19.1)	124 (28.4)	0.0002
Hypertension (%)	173 (13.1)	74 (17.0)	0.04
Bilirubin (umol/l)	10.3 (6.8; 13.7)	8.6 (6.8; 12.0)	<0.0001
LDL (mmol/l)	2.92 0.80	3.26 0.95	<0.0001
hs-CRP (mg/l)	0.9 (0.5; 1.8)	1.0 (0.5; 2.0)	0.01
Physical activity (%)	631 (47.7)	239 (54.8)	0.01

Data are numbers (percentage), means ± SD or medians (IQ range).

Figure 1 Odds ratios of prediabetes across quartiles of serum bilirubin levels in females and males

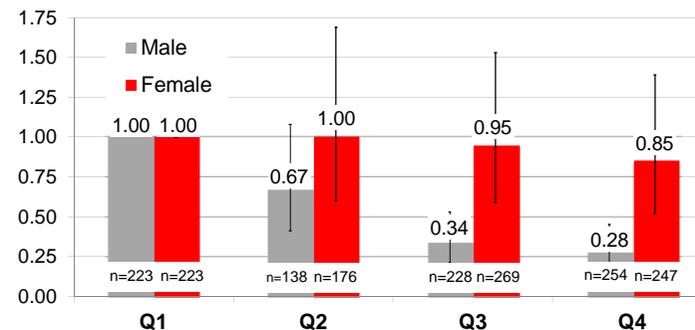


Table 2 Quartiles of serum bilirubin levels and risk of prediabetes

	Quartile 1 ≤ 6.8µmol/l	Quartile 2 6.8-10.3µmol/l	Quartile 3 10.3 - 13.7µmol/l	Quartile 4 > 13.7µmol/l	P for linear trend
Unadjusted model	Ref.	0.83 (0.61; 1.14)	0.59 (0.44; 0.79)	0.53 (0.39; 0.71)	<0.0001
Age- & sex adjusted model	Ref.	0.82 (0.59; 1.13)	0.55 (0.41; 0.74)	0.50 (0.37; 0.68)	<0.0001
Fully adjusted model	Ref.	0.83 (0.59; 1.17)	0.56 (0.41; 0.78)	0.51 (0.36; 0.71)	<0.0001

RESULTS

- Baseline characteristics are presented in **table 1**.
- Women had significantly lower bilirubin levels compared with men (median 8.55 (6.84; 11.97) vs. 10.26 (7.35; 13.68) µmol/L, p<0.0001).
- Multivariable logistic regression models of prediabetes risk across sex-specific quartiles of total serum bilirubin levels confirmed an inverse relationship between bilirubin and prediabetes (**Table 2**).
- In sex-stratified models, the ORs (95% CI) for prediabetes were 0.34 (0.23; 0.50), p<0.0001 per one unit increase in log-transformed bilirubin levels among men and 0.72 (0.51; 1.02), p=0.07 among women (p for interaction = 0.0006). Quartile-specific ORs confirmed these differential relationships and are displayed in **figure 1**.

CONCLUSION

- There is a highly significant inverse relationship of total bilirubin levels with prediabetes.
- These data support the concept that oxidative stress may be implicated in the early course of diabetes development.
- This effect may be stronger in men.