Diabetologia (2010) 53:2071–2072
DOI 10.1007/s00125-010-1834-5

LETTER

# Diabetes, cancer and iron

**L. Mascitelli · F. Pezzetta · M. R. Goldstein**

Received: 23 May 2010 / Accepted: 7 June 2010 / Published online: 23 June 2010


**Keywords** Cancer · Diabetes · Iron · Mortality · Prevention

*To the Editor*: Zhou and colleagues found that diabetes and prediabetes (impaired glucose tolerance and/or impaired fasting glucose) were independent risk predictors for all cancer death, particularly death from liver cancer [1]. However, the mechanisms underlying this detrimental association have not been fully elucidated. We suggest that increased body iron stores may predispose individuals to both diabetes and cancer.

Mounting evidence suggests that iron may play a role in the pathogenesis of type 2 diabetes and other hyperinsulinaemic syndromes [2]. Indeed, it has been shown that increased iron stores contribute to insulin resistance and hyperinsulinaemia by reducing hepatic insulin extraction and metabolism [3] and by decreasing glucose uptake in muscle [4]. In addition to the potential effect of iron on insulin action, insulin may also affect iron metabolism. In vitro data suggest that insulin is capable of redistributing the cellular pool of transferrin receptors, increasing the proportion at the cell surface, leading to increased cellular iron uptake in adipose tissue and the liver. This upregulating effect of insulin on iron uptake occurs concurrently with its effect on glucose uptake [2]. Epidemiological studies have reported a positive association between large body iron stores and the risk of type 2 diabetes [5]. Furthermore, induction of near iron deficiency in carbohydrate-intolerant individuals has been shown to improve insulin sensitivity [6]. An intervention study in patients with type 2 diabetes with elevated ferritin levels provided evidence that bloodletting resulting in a 50% reduction of serum ferritin concentrations (from 460 to 222 ng/ml) improved glycaemia and insulin sensitivity [7].

On the other hand, it is well known that individuals with a moderately elevated iron level have an elevated cancer risk [8]. In particular, an independent association between incidence of liver cancer and increased body iron level (approximated by serum transferrin iron saturation) has been observed [9].

In fact, a protective effect of iron loss against cancer risk has been confirmed in the iron (Fe) and Atherosclerosis STudy (FeAST), in which participants were randomised to iron reduction or control groups [10]. The FeAST study is the first randomised trial of the effects of induced stored iron reduction on cancer mortality. In the iron reduction group, the mean serum ferritin level declined from 122.5 to 79.7 ng/ml. Over 4.5 years, the risk of new malignancy was significantly lower in the iron reduction group than in the control group. Among patients with new cancers, those with iron reduction had lower cancer-specific and all-cause mortality rates, which were highly significant. The FeAST trial outcomes suggest that stored iron reduction may have a broad antitumour effect.

Therefore, it is highly plausible that iron, hyperinsulinaemia, insulin resistance and carcinogenesis are biologi-

L. Mascitelli (✉)
Comando Brigata alpina ‘Julia’, Medical Service,
8 Via S. Agostino,
Udine 33100, Italy
e-mail: lumasci@libero.it

F. Pezzetta
Cardiology Service, Ospedale di Tolmezzo,
18 Via Morgagni,
Tolmezzo 33028, Italy

M. R. Goldstein
Fountain Medical Court,
9410 Fountain Medical Court, Suite A-200,
Bonita Springs, FL 34135, USA

cally intertwined. It is important in future studies to systematically include assessments of the effects of the intervention on iron status in diabetic patients and to also investigate the particular effects of iron depletion on both diabetogenesis and carcinogenesis.

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.

## References


1. Zhou XH, Qiao Q, Zethelius B et al; for the DECODE Study Group (2010) Diabetes, prediabetes and cancer mortality. Diabetologia. doi:10.1007/s00125-010-1796-7
2. Rajpathak SN, Crandall JP, Wylie-Rosett J, Kabat GC, Rohan TE, Hu FB (2009) The role of iron in type 2 diabetes in humans. Biochim Biophys Acta 1790:671–681
3. Niederau C, Berger M, Stremmel W et al (1984) Hyperinsulinaemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation? Diabetologia 26:441–444
4. Merkel PA, Simonson DC, Amiel SA et al (1988) Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. N Engl J Med 318:809–814
5. Tuomainen TP, Nyyssonen K, Salonen R et al (1997) Body iron stores are associated with serum insulin and blood glucose concentration: population study in 1,013 eastern Finnish men. Diabetes Care 20:426–428
6. Facchini FS, Saylor KL (2002) Effect of iron depletion on cardiovascular risk factors: studies in carbohydrate intolerant patients. Ann NY Acad Sci 967:342–351
7. Fernandez-Real JM, Penarroja G, Castro A, Garcia-Bragado F, Hernandez-Aguado I, Ricart W (2002) Blood letting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. Diabetes 51:1000–1004
8. Stevens RG, Graubard BI, Micozzi MS, Neriishi K, Blumberg BS (1994) Moderate elevation of body iron level and increased risk of cancer occurrence and death. Int J Cancer 56:364–369
9. Ioannou GN, Weiss NS, Kowdley KV (2007) Relationship between transferrin-iron saturation, alcohol consumption, and the incidence of cirrhosis and liver cancer. Clin Gastroenterol Hepatol 5:624–629
10. Zacharski LR, Chow BK, Howes PS et al (2008) Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial. J Natl Cancer Inst 100:996–1002