Insulin resistance and increased risk for malignant neoplasms: confounding of the data on insulin glargine

J. M. Nagel · U. Mansmann · K. Wegscheider ·
J. Röhmhel

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To the Editor: Hemkens et al. [1] studied the risk of malignant neoplasms and mortality in patients treated with human insulin or with one of three insulin analogues. In vitro experiments [2] demonstrated a potential association of insulin analogues with an increased risk of malignancies. Epidemiological corroboration of the in vitro findings would have major implications for diabetic patients worldwide.

J. M. Nagel (✉)
Division of Endocrinology,
Beth Israel Deaconess Medical Center,
330 Brookline Avenue, ST 816,
Boston, MA 02115, USA
e-mail: jnagel@bidmc.harvard.edu

U. Mansmann
Institute of Medical Informatics, Biometry, and Epidemiology,
University of Munich, Marchioninstr.15,
81377 Munich, Germany

K. Wegscheider
Department of Medical Biometry and Epidemiology,
University Medical Center Hamburg-Eppendorf,
Martinistrasse 52,
20246 Hamburg, Germany

Present Address:
J. Röhmhel (✉)
Im Holze 36a,
28355 Bremen, Germany
e-mail: joachim.roehmhel@gmx.de

The German statutory health insurance fund is a comprehensive data source from which to generate results on drug safety if the data analysed are representative of the population of interest. Based on Fig. 1, the number of prevalent and incident users in the study by Hemkens can be calculated as follows: after exclusion of 74,468 patients using both insulin and an analogue, or bovine or porcine insulin, the remaining 248,264 patients were treated with insulin (human insulin 209,408; insulin aspart [B28Asp human insulin] 4,777; insulin lispro [B28Lys,B29Pro human insulin] 6,732; and insulin glargine [A21Gly,B31Arg,B32Arg human insulin] 27,347). The total number of patients excluded because of insulin treatment within 1 year prior to first prescription can be viewed as the number of prevalent users: 103,163. Subtracting these, the number of new insulin users (incident users) is therefore 145,101. The number of insulin users (prevalent patients) at 1 January 2001 ($n=103,163$) reported by Hemkens et al. [1] appears implausibly small compared with the number of new insulin users (incident patients) from 2001 to June 2005 ($n=145,101$). Even if the study had originally included the 74,468 patients using both insulin and an analogue or bovine or porcine insulin, less than 1% of nearly 18 million patients would be considered as prevalent patients at 1 January 2001. This figure seems to be an underestimate [3, 4].

The exclusion criterion ‘patients with an event date equal to the study inclusion date’ was not further discussed in the paper. But it seems surprising that for about 3% of the total population the first prescription for insulin is received the same day a cancer is diagnosed, indicating possible problems related to the dates of diagnosis.

Data quality is critical when administrative databases are used for pharmacoepidemiological investigations. How do the authors deal with implausibly high mean daily

doses or unexpected gaps in drug prescriptions? Was the algorithm to calculate doses defined prior to the analysis or adjusted to the data during analysis? Outpatient diagnoses have only been documented in the records of the German statutory health insurance fund since 1 January 2004. How do the authors take account of this? How do the authors explain the extremely short observation period (7.2 months per patient on average) in the high-dose insulin glargine group and the decrease in the human insulin groups which all could explain the increase in incidence rates with increasing dose?

Pocock and Smeeth [5] criticise the definition of the cohort and the use of calculated mean doses as baseline covariates in a Cox proportional hazards model. We would like to point to further problems in the report that lessen the credibility of the results.

How do the authors deal with competing risks? Is death just a non-informative censoring mechanism or does it indicate a patient's higher risk of malignant neoplasms? Furthermore, the issue of confounding is not appropriately discussed. A multivariate analysis per se does not remove confounding. Analytical tools [6] exist to disentangle confounding even after adjusting for a series of variables in a complex observational study. Sensitivity analyses would have allowed the authors to detect the extent to which the association was affected by confounding. We fear that this oversight may have given the false impression that the detrimental effect of possible confounding was ruled out.

Our main concern is that the study compares subsets of patients that cannot easily be compared. Patients with either type 1 or type 2 diabetes mellitus were included although the type and the frequency of malignancies associated with either disease are very different [7]. Patients with type 1 diabetes cannot sufficiently be treated with insulin glargine only. Therefore, the insulin glargine group consisted mainly of type 2 diabetic patients and, despite being the 'more healthy' collective, could be expected to have a higher rate of cancer incidence because of insulin resistance.

In the crude analysis, however, the overall cancer incidence and overall mortality rate in the insulin glargine group were significantly lower. The authors try to explain this observation as an imbalance in the distribution of dose groups: 'Because patients receiving combined therapy with insulin analogues and human insulin were excluded, the mean daily dose was much lower for glargine than for human insulin, and a slightly lower cancer incidence in the glargine group was found.' The observed mean daily doses differed strongly between the insulin groups (Electronic supplementary material [ESM] Table 1 in [1]). Any pathophysiological reasons for these imbalances are ignored by Hemkens et al. Instead, they compare the effect of dose subgroups of human insulin and three insulin analogues (insulin lispro, insulin aspart and insulin glargine) on a one-

to-one basis using a mathematical strategy to handle the imbalance by 'adjusting' for dose. Thus, they introduce—in addition to flaws mentioned by Pocock and Smeeth [5]—substantial imbalances in patient features within different dose groups. First, patients receiving basal therapy only with insulin (insulin glargine or human insulin) have type 2 diabetes during an earlier phase of the disease. They produce sufficient insulin to meet the (elevated) postprandial insulin needs. Ignoring the amount of intrinsic insulin production results in an unjustified calculatory excess in cancer incidence in the adjusted analysis. Second, patients with a need to take additional insulin to control postprandial high glucose levels may have type 1 or type 2 diabetes. They were deliberately excluded from the insulin glargine group, but not from the human insulin group, producing an unfair comparison on the basis of mean total insulin dose.

In line with our argument, no increased risk was found for the two short-acting analogues. These are more often used by patients with type 1 diabetes (judging by the lower frequency of concomitant use of oral glucose-lowering agents) without insulin resistance. Increased needs for insulin treatment reflect increasing insulin resistance, particularly in patients with type 2 diabetes, and many epidemiological studies have been able to demonstrate a link between insulin resistance and cancer [8].

Thus, the data presented by Hemkens et al. [1] support earlier findings that high doses of insulin, reflecting increasing insulin resistance, are associated with an increased risk of cancer. However, their study does not provide data or results convincing enough to warrant the scare of a safety concern regarding the use of insulin glargine by diabetic patients. The published measures of association are confounded and cannot describe real risks.

Duality of interest J. Röhmle has received honoraria for given lectures for the biostatisticians at Bayer-Schering Pharma and has served as a statistical consultant to Bayer-Schering Pharma, Basilea, Johnson&Johnson, and Stada. U. Mansmann was supported by sanofi-aventis (who manufacture insulin glargine) to review the methodological literature on meta-epidemiological studies of clinical trials. J. M. Nagel and K. Wegscheider have no duality of interest. Sanofi-aventis did not support this work either by writing or editorial help, and did not contribute to the final manuscript in any other way.

References

1. Hemkens LG, Grouven U, Bender R et al (2009) Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 52:1732–1744
2. Kurtzhals P, Schaffer L, Sorensen A et al (2000) Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 49:999–1005
3. Scherbaum WA, Kiess W (eds) (2004) *Epidemiologie und Verlauf des Diabetes mellitus in Deutschland*. Available from [www](http://www.diabetes-mellitus.de).

- deutsche-diabetes-gesellschaft.de/leitlinien/EBL_Epidemiologie_Update_2004.pdf, accessed 4 September 2009
4. Rathmann W, Giani G (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:2568–2569 author reply 2569
 5. Pocock SJ, Smeeth L (2009) Insulin glargine and malignancy: an unwarranted alarm. *Lancet* 374:511–513
 6. Jewell NP (2004) *Statistics for epidemiology*. Chapman & Hall/CRC, Boca Raton
 7. Zendejdel K, Nyren O, Ostenson CG, Adami HO, Ekblom A, Ye W (2003) Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst* 95:1797–1800
 8. LeRoith D, Novosyadly R, Gallagher EJ, Lann D, Vijayakumar A, Yakar S (2008) Obesity and type 2 diabetes are associated with an increased risk of developing cancer and a worse prognosis; epidemiological and mechanistic evidence. *Exp Clin Endocrinol Diabetes* 116(Suppl 1):S4–S6