Insulin Therapy and Cancer

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That diabetes is associated with an increased lifetime risk of developing malignancy is now well established (1,2). For some specific malignancies, explanation of that increased risk is possible, though usually unproven. For example, the marked increase in pancreatic cancer incidence in type 2 diabetes may or may not be due to misattribution of type of diabetes where the reality is secondary diabetes. Also markedly increased is hepatic malignancy—something that may be secondary to hepatic steatosis or, rather, hepatosteatitis and subsequent fibrotic/regenerative disease. Lesser increases in large-bowel malignancy are also found in association with obesity and modern low-residue high-fat diets, and both obesity and such diets are associated with diabetes (1,3). In contrast, it is notable that high-concentration insulin given repeatedly into the same injection site for many decades has not generated even one report of a subcutaneous sarcoma in >90 years in tens of millions of people.

Type 2 diabetes and other types of diabetes, once vascular damage is occurring, are inflammatory states, which may provide an environment for oncogenesis of some malignancies. However, the inflammatory state might also might provide enhancement of immune cancer surveillance mechanisms. The reduction of prostate cancer incidence is potentially explainable in the context of relative reduction in circulating testosterone levels in men with type 2 diabetes.

A second concern over diabetes and malignancy is regarding glucose-lowering therapies. However, only in the case of PPAR-$\alpha\gamma$ agonists is there reasonably strong data once information from preclinical studies, randomized controlled trials (RCTs), and observational studies is taken together (4–6). For insulin, the data are more complex to assess. Preclinical animal data of concern are limited to an analog with unusual receptor binding properties. However, mechanistic data do suggest mechanisms by which increased malignancy risk could operate, and this has raised concerns about some licensed insulin analogs, notably insulin glargine.

This review is meant to be an overview of the concerns surrounding insulin, with the intention of seeking the level of probability that endogenous or exogenous insulin could be contributing to malignancy risk in clinical practice and looking for research pathways to inform this further.

METHODS—Literature searching for this review was not systematic. Search terms around insulin, malignancy, and cancer and narrowed for specific areas to observational studies, randomized controlled trials, insulin therapy, growth promotion, and insulin analog(ue)s still revealed very large numbers of sources in the literature (>2,000,000), from which the reviewer then selected, with potential bias, papers of higher quality or interest and those more often quoted by other authors and supported by studies referred to from the initially identified reports.

In handling the evidence, I attempt to take the data from a study in the context of prior knowledge and asks the question, "How does this study shift the probability that such and such an effect is real to the extent that it should help determine routine clinical practice or promote further research activity?" The limitations of the available literature restrict the conclusions that can be made, as in any scientific review.

MECHANISTIC DATA—The existence of potential mechanisms by which a substance (in this case, insulin or derivatives) can promote malignancy does not by itself significantly raise concerns that such a problem will occur. Indeed, without other evidence, whether preclinical (animal studies), observational, or controlled studies, mechanistic data on how such an effect might occur provide very little indication of probability that it will occur in clinical practice. This is contrary to human intuition because the opposite approach, of attaching a mechanism to a described adverse event, provides a good opportunity for avoiding or ameliorating the event, and accordingly we instinctively give mechanistic explanations quite a lot or even excessive weight. As will be seen below, the evidence from animal and clinical studies for insulin being a causative factor in human malignancy is weak, so the mechanistic discussions that follow currently have limited clinical relevance.

Most of the potential mechanisms for insulin being a risk factor for cancer concern growth promotion. Studies looking for genotoxicity have been unsuccessful (7). There is no evidence that insulin regulates or affects expression of established oncogenes, including those of the tyrosine kinase family. Growth promotion could affect the lifetime clinical incidence of cancer by allowing protective cellular and immune surveillance mechanisms to be overcome. Furthermore, in the short term it might appear to increase the incidence rate of cancers by causing those already present to be detected sooner.

Two putative mechanisms may be identified. Firstly, and attracting much attention with regard of insulin therapy, is the cross-reactivity between binding for their respective receptors (and subtypes) of insulin and IGF-1 (8). Insulin is in any case, and distinct from its glucose-lowering activity, an anabolic hormone with actions on amino acid uptake and protein synthesis, which is the basis of its misuse by athletes. Of interest here is the existence of a growth-promoting (fetal) insulin receptor (A), which is

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sometimes overexpressed in tumors, notably breast malignancies, and of hybrid insulin–IGF-1 receptors (9,10). Furthermore, insulin receptor A has higher binding affinity for IGF-1, though it is still an order lower than for insulin (11). Higher concentrations of insulin receptor substrate 1 can be found in malignant tumors but are reported to be highest in those with benign outcome (12).

Clinically, the property that has raised concerns for insulins has been its IGF-1–to–insulin receptor binding affinity. However, as insulin is mainly cleared through its receptor, insulins with low insulin receptor affinity are present in the circulation in higher concentration than native human insulin—something that will also enhance IGF-1 receptor binding. Insulins of the B-terminal diarginyl series (i.e., B31-B32 diarginyl insulins) are of particular concern, as without other amino acid change they have an ~20:1 IGF-1:insulin receptor binding ratio compared with human insulin (8). However, even at this ratio it is debatable whether insulin would contribute significant growth factor activity compared with the tissue levels of IGF-1 itself, given that the latter has much higher affinity for its own receptor than does insulin and because it circulates at much higher concentrations than insulin (11).

Studies of malignancy rates in acromegaly have resulted in uncertainty as to whether malignancy is increased or not (13). A particular concern might, however, arise with breast cancers (other malignancies are less well studied), some of which have markedly enhanced expression of insulin or IGF-1 receptors (14,15).

The second mechanism of insulin growth promotion is less well documented but did result in mammary tumors in susceptible rats. Asp-B10 insulin is an unusual human insulin analog that had apparently markedly enhanced binding to hepatocytes in vitro. However, that may be an artifact of another receptor property of that insulin, namely, slow insulin receptor dissociation rate (16). It is hypothesized that this property might have been the cause of increased signaling down the mitogen-activated protein kinase pathway (and thus growth promotion and mitogenesis) rather than the phosphatidylinositol 3-kinase or CAP (Cbl-associated protein) pathways involved in metabolic signaling. Studies of other insulins suggest that this was a fairly unique property of Asp-B10 insulin; it is not a problem for any of the other human insulin analogs in clinical use, such as insulin glargine (17).

PROPERTIES OF INSULIN GLARGINE—Insulin glargine is an end-chain diarginyl insulin (see above) but additionally has a Gly-A21 amino acid substitution—a substitution that reduces relative IGF-1–binding activity (8). Accordingly (and dependent on the cell model used for testing) the ×20 increase in binding of the B-chain substitution is reduced to ×6 for insulin glargine itself (8). As noted above, this difference is unlikely to be significant in cancer-promoting terms, as recognized at the point of licensing, particularly as detailed receptor studies did not reveal any Asp-B10 insulin–like continued receptor signaling (17).

Diarginyl insulin is a natural product of endogenous insulin production and circulates in all people with an intact pancreas, though in very small amounts relative to insulin. Indeed, the diarginyl bond is a regular cleavage site in proteins, and many tissues contain peptidases to remove such residues, including subcutaneous tissue. This raises the question as to whether insulin glargine, during its long residence time in the subcutaneous tissues or after release from its insoluble subcutaneous complexes but before absorption, might be partly or largely degraded to the A21-Gly human insulin with low IGF-1 receptor binding. Indeed, this turns out to be the case, with three studies reporting that the overwhelming circulating species of insulin after subcutaneous glargine injection is its so-called M1 metabolite, A21-Gly human insulin (18–20).

OBSERVATIONAL STUDIES

Methodology and biases

Observational studies with insulin in people with type 2 diabetes often find that it is associated with worse outcomes and more deranged metabolism (whatever outcome is measured), as indeed is the case for malignancy (21). In some studies, it is recognized that for the most part, since insulin is used late in the therapeutic pathway, it is useful to adjust for age and duration of diabetes. Unfortunately, even this cannot control for biases introduced by people with other illness being in closer contact with the medical profession and the risk that in the complex disease environment the clinical site (e.g., university hospital) where insulin is started may be more likely to be using the latest glucose-lowering technologies (2). Observational studies should usually therefore be regarded as hypothesis generating.

Some studies have suggested insulin to be associated with lower rates of cancer and lower rates of progression to an extent that has been noted by commentators to be remarkable (22,23). Again, this is likely to be an association confounded by hidden factors; people presenting with cancer or progressing with disseminated disease will tend to be anorexic, such that if they have type 2 diabetes the need for therapies will be reduced.

Biases that can result in confounding effects include drug use indication bias, prevalent user bias, detection bias, and time-related biases. The potential for indication bias is very large in type 2 diabetes owing to the complexity of the condition and its association with obesity (and thus dietary change), cardiovascular risk factors, and inflammation. As a simple example, obesity and hyperglycemia are associated with malignancy and with insulin insensitivity—thus the earlier use of insulin and of insulin in higher doses. Indication bias might result in people subject to adverse health outcomes such as malignancies being more likely to come into contact with hospital-based care teams and then more likely to start diabetes therapies including insulin earlier than those continuing to be seen in family practice. This might account for the detection bias (high rates in early months falling rapidly thereafter) seen in some studies (24). Currie et al. (25) found that insulin users with cancer were more likely to have cardiovascular disease at diagnosis, confirming that they were not the same population as the comparator non-insulin users. Lind et al. (26) noted rapid falls in prostate cancer incidence over 5 years from abnormally high levels with duration of use of insulin glargine. This might then even apply to particular therapies if, for example, one group of practitioners were more likely to use insulin analogs than another using predominantly human insulins. Other issues surround contraindications and comparators; metformin, for example, has tended to be used less in anyone with liver, renal, or gut disturbance, so populations taking metformin tend to do better in observational cohorts for many types of outcomes. However, for cancer this was not confirmed in a meta-analysis of randomized controlled trials

(27). Additionally, metformin is usually prescribed early in the course of diabetes and insulin later, so studies need to adjust for duration of diabetes, which apparently was not done even in a recent database study (25).

Prevalent user bias can arise in various ways and sometimes can be as simple as poor ascertainment of when a drug is started in relation to an outcome (if, for example, the drug is started in the hospital but the first record is later from a prescription issued in family practice) (28). The issue of time-related biases in diabetes therapy studies has been discussed by Suissa and Azoulay recently (29).

Outcomes of studies

In the light of the above problems, can anything useful be concluded from published observational studies of cancer (insulin glargine is considered separately below) and insulin use? Even if they are taken to be hypothesis generating, the literature is quite contradictory as to associations of increased or decreased prevalence, incidence, or progression (28). Given these conflicting findings and the unresolved methodological issues discussed above, the best conclusion is perhaps that the studies as a whole do not contribute to clinical decision making in the management of people with diabetes, although individual studies are useful in contradicting the findings of others.

There does seem to be an improvement in methodological quality or attempts to address it in the last 5 years. The China/Hong Kong studies from Yang and colleagues are helpful in this regard, but as noted above the findings from some of these are surprisingly favorable with regard to insulin therapy to an extent that is difficult to understand mechanistically (2,22). Furthermore, study of oriental populations with BMI well below 30.0 kg/m^2 on average may not help to answer the underlying question of whether obese people with unphysiologically high (×2–8) endogenous with or without exogenous insulin exposure suffer a growth-promoting or other effect of insulin if they develop susceptible tumors. Boyle et al. (30) have recently published a detailed meta-analysis of breast cancer in diabetes, concluding that there may be a 27% increase in type 2 diabetes but not in type 1 diabetes or gestational diabetes mellitus where insulin use is universal or more common.

Insulin glargine

As noted above, the issues surrounding insulin glargine are not supported by mechanistic studies, but once raised the questions cannot be ignored (31). The RCT evidence is discussed separately below. The issue came to prominence with the publication of four studies in *Diabetologia*, which taken together suggested no malignancy association with glargine, despite being subject to some of the methodological issues discussed above (32–35). In one study, which suggested an overall but small benefit of association with insulin glargine use, the data were clearly flawed by the study populations having very different insulin dose use, meaning they were different noncomparable populations for unascertained reasons (32). In these circumstances, no adjustment for the limited range of covariates would help (propensity analysis might have gone someway to reducing biases, using pair matching for all available characteristics including dose), and therefore the authors' finding of increased dose-adjusted risk for glargine has very little value. In another of the four studies, specific site malignancy (breast) has increased association with glargine (34), but in the circumstance of no prior specific hypothesis and with multiple sites tested statistically without adjustment, this too has very low evidence impact.

A number of studies have attempted to address this area of investigation, and attention has been drawn to their limitations (36–38). Boyle and colleagues performed a detailed meta-analysis of the insulin glargine observational data. This was presented at the International Diabetes Federation annual meeting (2011) and American Diabetes Association Scientific Sessions (2012), and the presentations are available online (39,40). As such, they are not subject to formal prior peer review, while the activity was sponsored by the manufacturer of insulin glargine. Nevertheless, the analysis is comprehensive, and sensitivity analyses address such issues as allowing the effect of the Hemkens and colleagues dose adjustment to be understood within the context of the other published findings. Other studies presented in symposia at the American Diabetes Association Scientific Sessions 2012 from a U.S. insurance company and the Kaiser Permanente database reached similar conclusions: that there is no association with overall malignancy or with any specific tumor site, although even with meta-analysis there are limitations in the amount of data available for breast or any other single site cancer, and of course duration of exposure is limited by the introduction of insulin glargine from 2003. How such limitations should affect clinical practice is discussed below.

RCTs

Methodological issues

It might seem as though, as the gold standard of treatment comparisons, RCTs should be able to answer the questions posed here. However, there are also issues with the RCTs in this area. The most basic of these is that all but one of the studies (Outcome Reduction With Initial Glargine Intervention [ORIGIN]) (see below) were not set up to assess cancer outcomes, which thus were for the most part collected as serious adverse event (SAE) reports. In areas such as cardiovascular disease, this is recognized as being problematic, as investigators may not be sure what constitutes an event and may have limited access to diagnostic information from other medical services, perhaps from health events that happened to the patient in other cities. For malignancies, this may not seem to be such a problem, but when trawling through SAE and AE data it becomes obvious that there are problems with materials originating from study sites—not least in the diverse terminology used. Despite specification that malignancies should be SAEs, some are still reported as adverse events (mixed in with a large number of benign tumors), and the use of words like "neoplasm" often seems to be investigator solutions to not knowing the nature of a lesion. Liver metastases (or merely deposits on scans) give similar problems as to origin. Only rarely is some kind of post hoc adjudication of malignant events undertaken, often without recourse to retrospective inquiry for more details from investigator sites (a process that anyway is usually very unrewarding). Additionally, many RCTs are phase 3 studies of duration of <12 months, which may not give time for any drug effect to become manifested and often contribute less than three events per study.

Meta-analysis is in some minds given a magical aura to deal with the problems of RCTs. This is mostly not the case, as meta-analysis is only as good as the underlying data it considers, and problems such as heterogeneity of the

populations studied may even worsen that compared with the better RCTs alone. Ultimately, meta-analysis is only useful for the purpose of gaining power where the patient exposure in available studies is small—often thus being based largely on the short-term phase 3 studies with all their limitations.

RCT findings

However, the ORIGIN study, an RCT of insulin glargine versus standard care in persons ranging from prediabetic to taking two oral agents at entry, is useful in being of relatively high exposure, having sizeable participant numbers followed for a median of 6.2 years, and having adjudicated cancer outcomes (41). By studying insulin glargine, it effectively deals with the issues of both insulin and that specific analog. The findings were of no benefit or harm, with large numbers of events (953) and thus tight CIs for all cancer (95% CI 0.88–1.13) and deaths from malignancy (0.77–1.15) versus a mix of other glucose-lowering therapies used slightly less intensively. For specific malignancies, the results are inevitably less certain owing to smaller numbers, but the spread of findings on either side of a hazard ratio of unity points to no identifiable signal. Even for quite large CIs (say, up to an 80% increased risk as chosen by the U.S. Food and Drug Administration for cardiovascular events when licensing new medications), statistical power requires event numbers of >100 and absence of multiple testing, neither of which can be expected to be attained in our current RCTs for any one organ site malignancy. The weakness of the study is that diabetes duration at entry was relatively short (indeed, a small proportion of participants had just glucose intolerance) and BMI not as high as in some treated populations (mean <30.0 kg/m^2), so resulting insulin dose in the treated group was modest, even in those continuing insulin treatment at 6 years (end of study mean ~40 units/day). Accordingly, the study does not deal with the question of high exogenous insulin doses added to high endogenous secretion in the more markedly obese person.

A meta-analysis of the insulin glargine studies reported findings in both types of diabetes, against NPH insulin, and in both longer- and shorter-duration studies (42). The approach has all of the problems discussed above, with only one study (the retinopathy study) having duration of diabetes >1 year and that with limited participant numbers (n = 514 exposed) (43). Accordingly, with only 91 persons (glargine and comparator) experiencing a new malignancy, the upper CI was 1.36, while for specific site malignancies such as breast cancer the upper CI was >2.0. There was no signal for an increase in malignancy in the retinopathy study. Boyle and colleagues later extended these analyses of the RCTs reporting hazard ratios of 0.88 (95% CI 0.80–0.97) for glargine versus comparators, but suggested caution should be exercised in overinterpreting the results as indicating a small benefit (39,40).

CONCLUSIONS—Presently, it is difficult to conclude that there is any evidence of risk of malignancy from exogenous insulin of a size great enough to modify clinical practice decisions. Further studies might be directed at people who have already had one neoplasm (and therefore have a particularly high background risk), those with high background risk for other reasons (e.g., genetic makeup predisposing to breast cancer, exposure to asbestos), and those women whose breast cancers overexpress insulin receptor subtypes and IGF-1 receptors. However, the issue of high-dose insulin therapy has not been properly studied, and such people nearly always have high endogenous insulin secretion and some tendency to an enhanced inflammatory state, putting them at risk. It cannot presently be argued that any of the groups of people at higher risk should be denied the benefits of insulin therapy if they need it, particularly as nearly all other glucose-lowering therapies have other putative or real safety risks.

For insulin analogs, it might seem unwise to introduce and develop another diarginyl insulin where other approaches are possible, but insulin glargine–type molecules seem safe. An issue will arise if small-molecule insulin receptor agonists are developed: these might end up missignaling down the mitogen-activated protein kinase pathway as insulin AspB10 was presumed to do and, as such, will need careful and full preclinical and toxicological review, including avoidance of insulin receptor A binding. This will not be an easy undertaking, as overdosing of insulin kills animals from hypoglycemia, limiting the use of conventional toxicological studies.

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