Indian J Med Res 140, July 2014, pp 15-18

Perspective

Diabetic oncopathy - One more yet another deadly diabetic complication!

Diabetes epidemic worldwide is again certified by the International Diabetes Federation (IDF) Diabetes Atlas, 6th edition, recently. According to the IDF report[1], there are more than 382 million diabetes patients worldwide and India alone harbours more than 65 million. Patients with diabetes have an increased risk of developing a number of serious health problems. Consistently high blood glucose levels can lead to serious macrovascular complications affecting the heart and blood vessels and microvascular complications affecting eyes (diabetic retinopathy), kidneys (diabetic nephropathy), and nerves (diabetic neuropathy). It is important for physicians to understand the relationship between diabetes and its macro-and microvascular complications because the prevalence of diabetes continues to increase worldwide, and the clinical armamentarium for primary and secondary prevention of these complications is also expanding.

Diabetes and cancer

The relationship between diabetes and cancer has become a topical issue now. It was as early as in the year 1910, Maynard[2] reported the following: 'Cancer and Diabetes - both diseases have very much the same age distribution. They stand almost alone as being on the increase, while other causes of death show declining rates. The etiology of both diseases is obscure. Both being diseases of old age…if there were a common factor in the causation of the dual increase - a correlation between these diseases might be discovered'[2]. Cancer and diabetes are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age[3]. Patients with cancer and diabetes mellitus are frequently encountered in clinical practice. It is estimated that approximately 8 to 18 per cent of people with cancer have concurrent diabetes, probably because of the shared risk factors between the diseases and their increasing global prevalence[4]. Except for a few isolated studies in India[5], there is a lack of cohort studies on association of diabetes and cancer[6]. A recent Pune-based study by Sinha *et al*[7] observed that in a given population, there is an increase in the occurrence of certain cancer types under diabetic condition. This study emphasizes that the interplay between diabetes and cancer in Indian population may be complex and warrants futuristic detailed cohort studies.

'Diabetic oncopathy' - an emerging diabetic complication

Epidemiological data suggest that patients with diabetes have a higher risk of developing several types of cancer, including liver, pancreatic, colorectal, gynaecologic, and breast cancer. Does it imply 'diabetic oncopathy', as an emerging diabetic complication? Growing evidence suggests that glucose metabolism abnormalities can represent an independent risk factor for the development of specific cancers and can affect their prognoses. Increase in the risk of pancreatic cancer in individuals with diabetes relative to those without diabetes has been shown by several studies and meta-analysis[8].The interpretation of the causal nature of the association between diabetes and pancreatic cancer is complicated by the fact that abnormal glucose metabolism may be a consequence of pancreatic cancer and there could be a two-way relationship. However, the fact that diabetes was associated with an increased risk of pancreatic cancer among individuals who have had diabetes for at least five years implies that there is a cause for concern of pancreatic cancer in diabetics[9]. Therefore, there is an epidemiological evidence supporting a biological link between several types of cancer and type 2 diabetes, and there is a significantly higher cancer incidence and cancer-related mortality in those with diabetes[10]. Plausible mechanisms of the increased carcinogenesis and neoplastic proliferation in those with diabetes could be multifactorial, including the effect of hyperinsulinaemia, hyperglycaemia,

and inflammation[3]. While hyperinsulinaemia with stimulation of insulin growth factor-1 axis (IGF-1 axis) stimulates the proliferation of certain cancer cells by mechanisms that utilize both the phosphatidylinositol-3 kinase and mitogen-activated protein (MAP) kinase/ AKT signaling pathways, it is also a cell survival (anti-apoptotic) mechanism that enhances tumour cell migration and invasive capacity[11]. Though insulin is the main suspect, researchers are also exploring whether high blood glucose contributes to cancer because one trait of cancer cells is that these are adept at absorbing glucose from the blood with no need for insulin. In addition, inflammation is most important underlying issue both in diabetes and cancer. In order to understand the "bigger scientific picture", there is an imperative need to address the following questions: *(i)* is there a meaningful association between diabetes and cancer incidence or prognosis? If so, are the associations direct or indirect?; *(ii)* what risk factors could be common to both cancer and diabetes?; *(iii)* does diabetes increase the risk of cancer or do these simply share common risk factors?; *(iv)* what are the possible biological links between diabetes and cancer risk?; and *(v)* in what way diabetes treatments influence cancer risk or cancer prognosis or cancer protection?

Hyperinsulinaemia is a major culprit

Insulin is best known for its role as a homeostatic regulator of blood glucose, gluconeogenesis, and fatty acid metabolism in "metabolically active" tissues such as the liver, skeletal muscle, and adipose tissue. However, analysis of other physiological effects of insulin also suggests a highly conserved role of insulin as an important regulator of protein synthesis, cell growth, and proliferation. Widespread expression of the insulin receptor (IR) occurs in most classically "non metabolic" tissues such as breast, heart, brain, kidney, pancreas, and lung and in fibroblasts, monocytes, granulocytes, and erythrocytes[12]. Hyperinsulinaemia which is also a hallmark in type 2 diabetes is considered as a main culprit that connects the association of diabetes and cancer. A state of chronic hyperinsulinaemia and glucose intolerance may persist for prolonged periods prior to the development of hyperglycaemia and overt type 2 diabetes. In fact, a recent study has shown association of serum C-peptide concentrations with cancer mortality risk in pre-diabetes or undiagnosed diabetes[13]. Hyperinsulinaemia could potentially impact cancer progression by several mechanisms that might involve the innate and highly sensitive IR/ insulin growth factor (IGF)-IR signaling system. Insulin has a high affinity for IR-A and could thus act as a strong mitogenic signal and promote cell proliferation through its cognate receptor. Hyperinsulinaemia has been demonstrated to increase IGF-I bioavailability by both increasing hepatic growth hormone receptor expression, which leads to growth hormone mediated increases in IGF-I production by the liver[14] and by repressing hepatic production of IGF-binding proteins (IGFBP)[15]. Thus, this increase in IGF-I could lead to increased proliferative signaling via IR-A/IGF-IR hybrids and the IGF-IR. Hyperinsulinaemia also reduces hepatic secretion of sex hormone-binding globulin (SHBG)[16], which leads to elevated circulation of free estrogen which can act as a potential mitogen for estrogen-dependent cancers of breast and endometrial origin[17].

Conflicting results in relation to cancer and antidiabetic medication

Treatments for type 2 diabetes include insulin secretagogues (agents that stimulate insulin secretion) and insulin sensitizers (agents which sensitize tissues to insulin action). Later stages of type 2 diabetes necessitate the use of exogenous administration of insulin and insulin analogues. As many type 2 diabetes medications are used as long-term solutions for glycaemic control, but may have altered binding kinetics for the IR or increased affinity for the IGF-IR, it is important to investigate how anti-diabetic drugs that affect IR action could also affect the outcome of different kinds of cancer. Bowkar *et al*[18] have reported a significantly increased risk of cancer-related mortality in type 2 diabetes patients receiving sulphonylureas compared to patients receiving metformin. However, other studies report different effects on malignancies according to the type of sulfonylureas being used and hence, further clinical trials are required to establish how sulfonylurea treatments in type 2 diabetes could influence tumor incidence or progression. Conflicting studies (mostly using preclinical animal models and *in vitro* cell culture experiments), however, have reported the influence of thiazolidinediones (TZDs) in cancer development but clinical trials specifically investigating the relationship between cancer incidence and TZD usage in type 2 diabetics are also sparse[19] and the risk-benefit ratio also differs with different TZDs and different types of cancer[20]. The increased cancer risk so far claimed with TZDs appears to increase with duration of treatment; however, whether it is an effect that is common to all TZDs remains unclear.

Insulin is always used at a late stage of diabetes (insulin-requiring stage) when pancreatic β cells are

exhausted and most oral anti-diabetic agents fail to adequately control blood glucose. Therefore, indication bias may exist when it is used in patients with more co-morbidities that may also be linked to certain types of cancer. However, results from the recent ORIGIN trial found no difference in any cancer incidence in glargine users compared to regular insulin users over a period of six years[21], suggesting that the risk of breast cancer incidence and mortality from the use of insulin analogs, such as glargine, may be the same as that for human insulin. Similarly, a nationwide cohort study from Taiwan reported that glargine use did not increase the risk of overall cancer incidence as compared with human insulin[22]. A recent, large population-based study also negated the concern of a bladder cancer risk claimed to be associated with the commonly used human insulin[23]. While epidemiological studies have conflicting results regarding the risk of cancer with specific insulin analogues, it is also important that *in vitro* studies should also be interpreted with caution as these are of questionable physiological relevance. Therefore, further studies on the effect of treatment length on tumour occurrence may be necessary to assess the effects of long-term use of insulin(s) on different types of cancer risk.

The metformin promise

Several recent studies emphasize that treatment of diabetes and insulin resistance with dietary interventions, increased physical activity, and insulin-lowering drugs, such as metformin, may improve prognosis and responsiveness to anti-cancer treatments in patients with diabetes and cancer. Metformin which is an inexpensive, well-tolerated oral agent that is commonly used in the first-line treatment for type 2 diabetes worldwide, has also become the focus of intense research as a potential anti-cancer agent. The mechanism of actions of metformin is ever-evolving and it has been demonstrated that it inhibits hepatic gluconeogenesis, reduces insulin resistance and hyperinsulinaemia, improves glycaemic control, and decreases inflammatory responses, thus avoiding the potential tumor-promoting effect(s). Some *in vitro* and *in vivo* studies further demonstrated that metformin might have direct antitumour activity by inhibiting cancer cell proliferation and colony formation, inducing cell cycle arrest and apoptosis and suppressing xenograft tumour growth in mouse models[24]. Although activation of AMP-activated protein kinase (AMPK) is the key molecular mechanism by which metformin treatment brings about a wide range of metabolic benefits, recent studies[25] imply that metformin could also work independent of AMPK and through mechanisms involving the mitochondrial metabolism, glucagon receptor signaling, cyclic AMP production, and inhibition of mammalian target of rapamycin complex-1 (mTORC1). Results of human observational studies and meta-analyses suggest that treatment with metformin in diabetic patients is associated with reduced cancer risk or cancer mortality compared with other glucose-lowering therapies[26]. Patients with type 2 diabetes have increased cancer risk and cancer-related mortality, which can be reduced by metformin treatment. However, it is unclear whether metformin can also modulate clinical outcomes in patients with cancer and concurrent type 2 diabetes. In a recent meta-analysis, metformin has been shown to be associated with survival benefit in cancer patients with concurrent type 2 diabetes[24]. Another meta-analysis by Zhang and Li[27] also support the hypothesis that metformin improves the survival for cancer patients with concurrent diabetes, particularly for ovarian, pancreatic and colorectal, and endometrial cancer.

Conclusions

In the scenario of ever increasing prevalence and incidence of diabetes, it is important to address all the important clinical questions across the spectrum of diabetic complications including the so-called '*diabetic oncopathy'*. There is a need for a focused and directed approach towards novel preventive, diagnostic and therapeutic strategies and should be attempted through multidisciplinary and holistic approaches combining basic bench-top research with human physiology and clinical studies. At present, there is no clear consensus as to whether or not a particular antidiabetic drug is associated with cancer risk. It is, therefore, essential that diabetes patients focus attention on maintaining favourable glycaemic control following their physicians' instructions. In the era of treatment selectivity and molecular-targeted anti-cancer drugs, the accumulating evidence of common pathways linking cancer and diabetes is increasingly pointing the way forward for novel therapeutic avenues. Although there are challenges in translating preclinical findings to the clinical setting, the accumulation of evidence has been sufficient to justify initiation of long-term clinical trials of metformin as an anti-cancer agent in the clinical setting. India recently launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS) (http://www.nhp.gov.in/npcdcs). This underscores the visionary need for linking of cancer with diabetes as a part of an integrated programme for research, prevention and therapy. It is suggested that grant-funding mechanism (both national and

international) should not be any more biased towards individual diseases thereby influencing researchers to channel their efforts on one disease at a time. India has a strong medical infrastructure and biomedical research base attempting cancer biology studies with the help of oncologists while better understanding on the aetiology of diabetes is studied with the help of diabetologists. Irrespective of their domains, researchers studying the molecular pathogenesis of diabetes and cancer should foster collaborations on a common cell and tissue biology/ disease-biology platform. The time has also come to overcome the conventional tunnel vision that results in two diseases being treated by separate clinicians, and to move towards a comprehensive approach that is ideally treated by future *'diabetoncologists'*.

M. Balasubramanyam
Madras Diabetes Research Foundation (MDRF)
No. 4 Conran Smith Road, Gopalapuram
Chennai 600 086, India
balusignal@gmail.com; drbalu@mdrf.in

References

1. International Diabetes Federation (IDF). *Diabetes atlas*, 6th ed. Brussels, Belgium: IDF; 2013. p. 1-155.
2. Maynard GD. A statistical study in cancer death-rates. *Biometrika* 1910; *7* : 276-304.
3. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, *et al*. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; *33* : 1674-85.
4. Richardson LC, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Prac Oncol* 2005; *2* : 48-53.
5. Auluck A. Diabetes mellitus: an emerging risk factor for oral cancer? *J Can Dent Assoc* 2007; *73* : 501-3.
6. Amudhan S, Krishnan A. Diabetes mellitus: a risk factor for cancer and non-vascular disease deaths too. *Natl Med J India* 2011; *24* : 222-4.
7. Sinha A, Kumar R, Pawar B, Bhide A, Javadekar SS, Vijayakumar MV, *et al*. Population-based estimation of mortality and occurrence of cancer in patients with and without diabetes in Pune. *Curr Sci* 2013; *105* : 486-91.
8. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, *et al*. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer* 2011; *47* : 1928-37.
9. Elena JW, Steplowski E, Yu K, Hartge P, Tobias GS, Brotzman MJ *et al*. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Cancer Causes Control* 2013; *24* : 13-25.
10. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: Review of the epidemiological evidence. *Cancer Sci* 2012; *104* : 9-14
11. Malaguarnera R, Belfiore A. The insulin receptor: a new target for cancer therapy. *Front Endocrinol (Lausanne)* 2011; *2* : 93.
12. Kaplan SA. The insulin receptor. *J Pediatr* 1984; *104* : 327-36.
13. Hsu CN, Chang CH, Lin YS, Lin JW, Caffrey JL. Association of serum C-peptide concentrations with cancer mortality risk in pre-diabetes or undiagnosed diabetes. *PLoS One* 2013; *8* : e55625.
14. Rhoads RP, Kim JW, Leury BJ, Baumgard LH, Segoale N, Frank SJ, *et al*. Insulin increases the abundance of the growth hormone receptor in liver and adipose tissue of periparturient dairy cows. *J Nutr* 2004; *134* : 1020-7.
15. Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; *4* : 579-91.
16. Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate AM, Fabbri R, *et a*l. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism* 1991; *40* : 101-4.
17. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. *Oncogene* 2004; *23* : 6379-91.
18. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006; *29* : 254-8.
19. Mamtani R, Haynes K, Bilker WB, Vaughn DJ, Strom BL, Glanz K, *et al*. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. *J Nat Cancer Inst* 2012; *104* : 1411-21.
20. Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM, Chan KA. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. *Hepatology* 2012; *55* : 1462-72.
21. Origin Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, *et al*. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012; *367* : 319-28.
22. Chang CH, Toh S, Lin JW, Chen ST, Kuo CW, Chuang LM, *et al.* Cancer risk associated with insulin glargine among adult type 2 diabetes patients--a nationwide cohort study. *PLoS One* 2011; *6* : e21368.
23. Tseng CH. Human insulin does not increase bladder cancer risk. *PLoS One* 2014; *9* : e86517.
24. Yin M, Zhou J, Gorak EJ, Quddus F. Metformin is associated with survival benefit in cancer patients with concurrent type 2 diabetes: a systematic review and meta-analysis. *Oncologist* 2013; *18* : 1248-55.
25. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clin Sci (Lond)* 2012; *122* : 253-70.
26. Soranna D, Scotti L, Zambon A, Bosettic C, Grassi G, Catapano A, *et al*. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 2012; *17* : 813-22.
27. Zhang ZJ, Li S. The prognostic value of metformin for cancer patients with concurrent diabetes- a systematic review and meta-analysis. *Diabetes Obes Metab* 2014; *16* : 707-10.