Review Article

Diabetes Mellitus and Oncology

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The growing incidence of diabetes mellitus as a multi-system metabolic syndrome with potentially lethal complications has made it a leading killer disease globally. This article will deal with the implications of diabetes mellitus on yet another major killer disease i.e. cancer. The problems will be dealt under the following heads.

1. Diabetes Mellitus in Pancreatic Malignancy
2. Diabetes Mellitus in Non-Pancreatic Malignancy
3. Diabetes Mellitus as a Paraneoplastic Syndrome
4. Diabetes Mellitus as a Complication of Cancer Therapy
5. Diabetes Mellitus as a mere association with cancer

Diabetes Mellitus in Pancreatic Malignancy

Primary tumours of the pancreas have an unique association with diabetes mellitus.[1] Diabetes has been described as both a "cause and effect" of carcinoma of pancreas. Estimates of incidence of diabetes mellitus in carcinoma of pancreas hovers around 20-60%.[1] The pathogenesis of diabetes in carcinoma pancreas could be due to several factors: (1) recurrent pancreatitis leading to fibrosis, (2) direct infiltration of the islet cells[2], (3) hereditary type of diabetes mellitus with its potential risk for pancreatic cancer, (4) autoantibodies against insulin and beta islet cells [3], (5) islet associated amyloid peptide synthesized by pancreatic cancer cells can produce impaired glucose tolerance.[4]

However, diabetes mellitus predates the diagnosis of carcinoma-pancreas by at least 2 years or so.[5] Some studies strongly consider diabetes mellitus as a promoting factor for pancreatic cancer although this is controversial. An Italian study clearly shows that diabetes mellitus is not a risk factor for pancreatic cancer but only a consequence of.[6] In pancreatic adenocarcinoma, the commonest pancreatic cancer, a basic defect in beta cell function has been eliminated as evidenced by inappropriate response to insulin and to glucagon.[7]

Some studies also suggest that the severity of diabetes mellitus does not correspond to the tumour stage or size of the pancreatic cancer. However curative surgery improves the glycaemic status.[8] Careful search for pancreatic carcinoma in new onset diabetes mellitus in elderly and sudden weight loss in NIDDM patients with suspected secondary failure to OHA have proven worthwhile in the diagnosis of cancer pancreas.[9]

Insulin has been identified as an important tumour growth promoter in cancer of pancreas as evidenced by presence of high-affinity insulin receptors and a dose dependent increase in pancreatic cell proliferation.[10] In addition the pancreatic tumour mass itself produced certain soluble entities that cause hyperglycaemia in vivo. These factors exert their diabetogenic effect by non-immune mechanisms and act at both the pancreatic level as well as the peripheral tissue level.[11] Carcinoma of pancreas and pancreatitis have an unique relationship in that 1. Patients with acute or chronic pancreatitis of any etiology are not a higher risk for developing cancer, 2. Patients with cancer pancreas have multiple episodes of acute clinical or subclinical pancreatitis with elevated enzymes. 3. Histopathological pancreatitis is inevitable in cancer of pancreas. Levels of Insulin like Growth Factor -1 (IGF - 1). I has been found to be elevated in pancreatic cancer and affects glucose homeostatis. Interluekin-1α is increased and Interleukin-1β is decreased in cancer pancreas with metastasis.[12]

Secondaries in the pancreas are by itself rare and studies are yet to confirm the evidence of diabetes mellitus in patients with secondaries to the pancreas from other malignancies.

Diabetes Mellitus in Non-Pancreatic Malignancy

1. *Diabetes Mellitus in Intestinal Endocrine Tumours*

a. *Gastrinoma* : Patients with gastrinoma especially those with extensive ulceration present with dia-

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betes mellitus as an additional complication.[13] Diabetes show a pseudo-Zolliger-Ellison syndrome characterised by hypergastrinemia with diminished or normal acid output.

b. *VIP Syndrome* : Patients show persistent hyperglycaemia which is probably due to the high portal venous Vasoactive Intestinal Polypeptide (VIP) levels which induces extensive glycogenolysis in the liver. Although no defect is noted in the beta islet cells or peripheral tissues, the hyperglycaemia in these situations is difficult to control.

c. *Glucagonoma* : Tumours producing glucagon - the natural antagonist of insulin action - produces mild diabetes in about 80% of patients.[14] The glucose intolerance in glucagonoma is related to the size of the tumour mass and the extent of metastasis. Larger hepatic metastases tend to have higher glucose levels subsequent to:

1. Diminished liver reserve to handle and metabolize glucagon.

2. Abnormal glucagon species with variable potency.

d. *Somatostatinoma* : The universal inhibitor hormone - somatostatin[15] when abundant, as in somatostatinoma, inhibits insulin release and produces diabetes mellitus.

e. *Pancreatic Polypeptidoma* : Diabetes is less common in the syndrome of excessive pancreatic polypeptide secreting tumour, which by itself, is rare.

f. *Neutrotensinoma* : Occasionally, diabetes has been described in this relatively rare tumour of APUD cells.

2. *Diabetes Mellitus in Other Systemic Malignancies*

a. *Diabetes in Pituitary Tumours* : Acromegaly produced by somatotrophic tumour is associated with glucose intolerance since the GH is an important counter-regular to insulin action.[16] In excess, the same produces its diabetogenic effect resulting in either Impaired Glucose Tolerance or frank diabetes mellitus.

b. *Diabetes in Lung Cancer* : Patients with small cell lung cancer develop diabetes mellitus during the illness due to growth hormone dysregulation.[17] This has been attributed to elevated IGF binding proteins which leads to disruption of IGF-I regulation of GH secretion and glucose homeostatis.

c. *Diabetes and Breast Cancer* : Although women with family history of diabetes had a higher prevalence of risk factors for breast cancer, no clear evidence suggests a definite association. However our own clinical observations (unpublished data) suggests that the prevalence of diabetes is high in women who have completed chemotherapy for breast cancer probably secondary to changes in the liver and further studies are needed on this aspect.

d. *Diabetes and Hepatobiliary Cancer* : Some studies, consider diabetes as a statistically significant risk factor for primary hepatic and billiary cancer.[18]

e. *Diabetes and Colorectal Cancer* : Delayed stool transit and elevated fecal bile acid levels associated with hyperglycaemia and diabetic autonomic neuropathy in NIDDM predisposes to colorectal cancer. However the presence of diabetes mellitus does not increase the fatality risk in colorectal cancer.[19] In vitro studies suggest that IGF-I stimulates colonic tumour cells.

f. *Diabetes in Renal Cell Cancer* : International renal cell cancer study[20] suggests that the relative risk of renal cell cancer was higher in diabetics after adjusting for age, sex and body mass index.

g. *Diabetes in Ovarian Cancer* : Diabetics do not carry any additional risk to develop cancer overy according to Parazzinni *et al.*[21] However, hyperlipidemia (common to diabetes mellitus) causes an inverse relationship with the risk of cancer.

h. *Diabetes in Cancer of Endometrium* : Endometrial cancer, now a leading cancer in women according to various studies is more common in diabetes.[22] Diabetes mellitus in an individual risk factor has been accepted widely and a screening schedule for such patients has been suggested to identify cancer of endometrium in its preneoplastic stage itself.

i. *Diabetes in Cancer of Prostrate* : A pilot study conducted in the USA suggests that diabetics carry very low risk for cancer of prostrate.[23] Although the basis is unclear, the low testostorone levels in diabetics accounts for this advantage.

j. *Diabetes in Haematological Malignancies* : Extranodal non-Hodgkin's lymphoma has been described to be associated with NIDDM by various studies.[24] However there are equal number of studies which refute the same. The prevalence of diabetes is high in patients with extra-nodal lym-

phoma especially those originating from the head, paranasal sinuses, central nervous system and orbit. The presence of genetic association between the extra-nodal lymphoma and the locus of NIDDM has been postulated as the cause of such an association.

III. Diabetes as a Paraneoplastic Syndrome

Endocrine paraneoplastic syndromes are many but the incidence of diabetes or IGT remains less common. Diabetogenic effect exerted by hormones like growth hormone, glucagon and VIP have been described as paraneoplastic manifestations of cancer. The most dramatic effect is by ACTH and related peptides that produce glucose intolerance especially in cancers of lung, thymus, pancreas and carcinoid. A rare phenomenon of paraneoplastic somatostatin induced diabetic ketoacidosis in a patient with bronchogenic carcinoma has been described. Insulin resistance occurring in some patients with cancer appears to be related to TNFα which inhibits signalling at the insulin receptor level and blocking its biological action.

IV. Diabetes Mellitus as a Complication of Cancer Therapy

Antineoplastic drugs like asparginase, steroids and hormones are certain common drugs used in the treatment of cancer which produce impaired glucose tolerance and sometimes frank diabetes mellitus. Interleukin-2 and α interferon combination used in cancer therapy either initiates or worsens diabetes mellitus.[25]

V. Diabetes as a Mere Association with Cancer

Certain genetic cancer syndromes are associated with diabetes mellitus. Bloom syndrome for example, is associated with DNA repair defects and diabetes mellitus. Brunzel's syndrome is a rare example characterised by cystic angiomatosis of soft tissue and bone with non-ketotic early onset diabetes mellitus and insulin resistance.

References

1. **Balkau B, Barrett Connor E, Eschwege E.** Pancreatic cancer and diabetes. *New England Journal of Medicine.* 1994; 331 : 1526-8.
2. **Evans JP, Burke W, Chen R, Bennet RL, Schmidt RA, Dellinger EP, Kimmey M, Crispin D, Brentnall TA, Byrd DR.** Familial pancreatic adenocarcinoma associated with diabetes mellitus. *Journal of Medical Genetics* 1995; 3295 : 330-5.
3. **Syrigos KN, Konstantoulakis MM, Fyssas I, Katsflambros N, Golemnatis BC.** Autoantibodies against insulin and beta islet cells in pancreatic adenocarcinoma. *International Journal of Cancer* 1996; 66 : 624-6.
4. **Permert J, Larsson J, Westermark P, Adrian TE.** Islet associated polypeptide in patients with cancer and diabetes mellitus. *New England Journal of Medicine* 1994; 330 : 313-8.
5. **Noy A, Bilezikian JP.** Diabetes and pancreatic cancer : Clues to early diagnosis of pancreatic malignancy. *Journal of Clinical Endocrinology and Metabolism* 1994; 99 : 1223-31.
6. **La-Vecchia C, Negri E, Franceschci S, D'Avanzo B, Boyle P.** Case controlled study of diabetes mellitus and cancer risk. *British Journal of Cancer* 1994; 70 : 950-3.
7. **Basso D, Plebani M, Fogar P, Bel-Favero G, Briani G, Meggiato T, Panozzo MP, Ferrara C, D'Angeli F, Burlina A.** Beta cell function in pancreatic adenocarcinoma. *Pancreas* 1994; 9 : 332-5.
8. **Fogar P, Pasquali C, Basso D, Sperti C, Panozzo MP, Tessari G, D'Angeli F, Del-Favero G, Plebani M.** Diabetes in pancreatic cancer follow up. *Anti Cancer-Research* 1994; 14 : 2827-30.
9. **Girelli CM, Reguzzoni G, Limido E, Savastano A, Rocca F.** Pancreatic carcinoma; Difference between patients with and without diabetes. *Recent Progress in Medicine* 1995; 86 : 143-6.
10. **Fisher WE, Boros LG, Schirmer WJ.** Reversal of enhanced pancreatic cancer growth in diabetes by insulin. *Surgery* 1995; 118 : 453-7.
11. **Basso D, Brigatto L, Veronesi A, Panozzo MP, Amadori A, Plebani M.** Pancreatic cancer cell line MIA PaCa2 produces one or more factors able to induce hyperglycaemia in SCID mice. *Anticancer Research* 1995; 15 : 2585-8.
12. **Basso D, Plebabi M, Fogar P, Panozzo MP, Meggiato T, D-Paoli M, Del-Favero G.** IGF-I, IL-α, 1 β in pancreatic cancer : Role in tumour invasiveness and associated diabetic mellitus. *International Journal of Clinical Lab Research* 1995; 25 : 40-3.
13. **Ellison EC, Carey LC, Sparks J, O'Donsio TM, Mekhjan HS, Fromkes JJ, Caldwell JH, Thomas FB.** Early Surgical Treatment of Gastrinoma. *Americal Journal of Medicine* 1987; 82-17.
14. **Montenegro F, Lawrence GD, Macon W, Pass C.** Metastatic glucagonoma : Improvement after surgical debulking. *American Journal of Surgery* 1980; 139 : 424.
15. **Gando PO, Weir GC, Soeldner JS, Legg MA, Chick WL, Patel YC, Ebeid AM, Gabbay KH, Reichilin S.** Somatostatinoma : A somatostatin containing tumour of the pancreas. *New England Journal of Medicine* 1977; 296.
16. **Hennessey JV, Jackson IM.** Clinical features and differential diagnosis of pictiutary tumours withemphasis on acromegaly. *Clinical Endocrinology and Metabolism* 1995; 9 : 271-314.
17. **Reeve JG, Morgan J, Clarke PM, Bleehen NM.** ICF and IGF binding protein in GH regulation and associated glucose tolerance in small cell lung cancer patients. *European Journal of Cancer* 1995; 31E : 1455-60.
18. **Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A.** Excess risk of primary lung cancer in patients with diabetes mellitus. *Journal of National Cancer Institute* 1996; 20 : 1472-7.
19. **Will JC, Galuska DA, Vinicor F, Calle EE.** Diabetes and colorectal cancer risk. *American Journal of Epidemiology*

1998; 9 : 816-25.

20. **Schlehofer B, Pommer W, Mellemgaard A, Stewart JH, Mccredie M, Niwa S, Lindblad P, Mandel JS, Mclaughlin JK, Wahrendorf J.** International renal cell cancer study : role of medical and family history. *International Journal of Cancer* 1996; 66 : 723-6.
21. **Parazzini F, Moroni S, La-Vecchia C, Negari E, Dal-Pino D, Bolis G.** Ovarian cancer risk and history related medical condition linked with female hormones. *European Journal of Cancer* 1997; 10 : 1634-7.
22. **Burke TW, Fowler WC, Morrow CP.** Clinical aspects of risk in women with endometrial cancer. *Journal of Cell Biochemistry - Supplement* 1995; 23 : 131-6.
23. **Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC.** Diabetes Mellitus and risk of prostrate cancer. *Cancer* 1998; 9 : 3-9.
24. **Toshiki N, Manabe Y, Kono M, Murayama T, Matsui T, Chihara K.** NIDDM and non-Hodgkin's lymphoma. *British Medical Journal* 1994; 9 : 1269.
25. **Whitehead RP, Hauschild A, Christophers E, Figlin R.** Diabetes mellitus in cancer patients treated with combination of IL-2 and α-IFN. *Cancer* 1995; 10 : 45-51.