 DOI: 10.5958/2394-6792.2016.00129.0

Association of Hypertension and Diabetes Mellitus with non-Hodgkin lymphoma - A hospital based study of 410 cases

Vijayshree Shivappa Neeravari[1,*], Doddappa Malleshappa Bannigidad[2], Lakshmi Rao[3]

[1]Assistant Professor, [2]Tutor, Dept. of Pathology, Koppal Institute of Medical Scienes, Karnataka, [3]Professor & Senior Consultant, Armed Forces Hospital, Mascat

***Corresponding Author:**
Email: drvijayashreen@gmail.com

Abstract

Several studies have found increased association of Diabetes Mellitus(DM) and Hypertension(HTN) in patients with non-Hodgkin lymphoma (NHL). We determined association of Diabetes Mellitus and Hypertension in 410 Non-Hodgkin lymphoma (NHL) patients diagnosed and treated in our institution.

Results: 8.5% of NHL cases were associated with diabetes Mellitus. Among NHL patients with diabetes Nodal NHL were commoner than the Extranodal NHL. The most common subtype was Diffuse Large B Cell Lymphoma (DLBCL) followed by Follicular lymphoma (FL) with a frequency of 57.14% and 17.14% respectively.

Hypertension was associated with 9.5% of NHL cases. Among the hypertensive patients, Extranodal NHL were more common with DLBCL being the most commonest subtype, followed by follicular lymphoma with a frequency of 56.4% and 20.5% respectively.

Conclusion: Diabetes Mellitus and Hypertension are associated with development of NHL either directly or due to drugs used in the treatment. Further studies are required to identify the specific drugs involved in the development of NHL especially in the Asian populations where prevalence of diabetes and Hypertension has increased in the recent years.

Keywords: Hypertension, Diabetes Mellitus, Non-Hodgkin lymphoma.

Introduction

The overall incidence of non-Hodgkin lymphoma (NHL) is relatively low in Asians, its incidence in Indians, Japanese, and Chinese (in Shanghai, China, and Singapore) are increasing since 1970s in parallel with other ethnicities in Europe, Australia, and America.[1,2] The etiology of NHL is not completely understood. However, immune dysfunction, viral infection and chronic inflammation are said to be associated with increased risk of developing NHL.[3,4] In addition, patients over 60 years of age can have hypertension and diabetes mellitus as co-morbid conditions, which can further complicate the understanding of pathogenesis of NHL.[5]

The prevalence of diabetes has increased over the last few decades.[6] Diabetes Mellitus has been associated with increased risk of several malignancies, including NHL, endometrial, ovarian, breast, gallbladder, liver, colonic, and pancreatic cancer [7] but its relationship with NHL is unclear. Individuals with diabetes are believed to develop NHL in two possible ways, one altered immune function and the other exogenous insulin. Insulin growth factor –I(IGF-I) causes cell proliferation, lack of apoptosis and cell metastasis[8], phenomena involved in the development and progression of malignancies. An association between diabetes and NHL was initially reported 40 years ago.[9] Since then, several studies have been conducted with inconsistent results.

Hypertension is associated in the development of several malignancies including lung, breast, skin, colon, stomach, bladder, rectum, prostate, pancrease, osephagus, ovary, cervix, kidney, melanoma, leukemia, myeloma and NHL.[10] Though, antihypertensive treatment decreases cardiovascular morbidity and mortality malignancy is one of the most common extra-cardiovascular causes of death in hypertensives. Several antihypertensive agents have been implicated in development of NHL and related death.[11] Several studies have been conducted to determine the association of hypertension and NHL with inconsistent results.

Materials and Methods

Total of 410 Cases of NHL diagnosed and treated at KMC, Manipal were identified by computerized record linkage and patient case sheets. Tumors were classified according to the WHO-2008 NHL classification. Individual records were matched using name, sex and indeterminate matches resolved by manual review. Diabetes was diagnosed with fasting sugar levels of >110mg/dl and post prandial sugar level of >140mg/dl. Hypertension was diagnosed using three readings with values >140/90mm Hg. The objective of this study was to estimate the association of diabetes and Hypertension with the development of NHL.

Result

Table 1: Association of Hypertension, and Diabetes mellitus with NHL in various studies compared with the present study

	Present study	Alexander et al[12]	Bilora et al[13]
Diabetes Mellitus	8.5	6	1.6
Hypertension	9.5	-	2.4

Table 2: Frequency of subtypes of NHL in Diabetic and Hypertensive patients

Diabetes (8.5%)			Hypertension (9.5%)		
Nodal (54.2%)	DLBCL	9(25.7%)	Nodal (43.5%)	DLBCL	8(20.5%)
	FL-G1	1(2.8%)		FL-G1	3(7.6%)
	FL-G2	4(11.4%)		FL-G2	4(10.2%)
	FL-G3A	2(5.7%)		FL-G3A	2(5.1%)
	MZL	1(2.8%)			
	MCL	1(2.8%)			
Extranodal (45.7%)	DLBCL	11(31.4%)	Extranodal (56.5%)	DLBCL	14(35.8)
	PGL	2(5.7%)		P-GL	2(5.1%)
	PCNSL	1(2.8%)		P-CNS-L	1(2.5%)
	AITCL	1(2.8%)		MALT	1(2.5%)
	CTCL	1(2.8%)		AITCL	2(5.1%)
	MALT	1(2.8%)		PTCLU	1(2.5%)
				MF	1(2.5%)
Total		35			39

DLBCL-Diffuse Large B cell Lymphoma, MF-Mycosis fungoides, FL-Follicular lymphoma, AITCL-Angioimmunoblastic T cell lymphoma, PCNSL- Primary CNS lymphoma, PGL- Primary gastric lymphoma, MALT- Mucosa associated lymphoid tissue, MZL-Marginal zone lymphoma, MCL-Mantle cell lymphoma, PTCLU- Peripheral T cell lymphoma, CTCL- Cutaneous T cell lymphoma.

In the present study 8.5% of total NHL cases were associated with diabetes Mellitus. Among NHL patients with diabetes, Nodal (54.2%) NHL was commoner than the extranodal (45.7%) NHL (Table 1). The most common subtype was Diffuse Large B Cell Lymphoma (DLBCL) followed by Follicular lymphoma (FL) with a frequency of 57.14% and 17.14% respectively (Table 2). Other nodal lymphomas associated were Marginal zone lymphoma and Mantle cell lymphoma each with a frequency of 2.8% respectively. Other Extranodal lymphomas associated were Angioimmunoblastic T cell lymphoma, Primary CNS lymphoma, Primary gastric lymphoma, Mucosa associated lymphoid tissue and Cutaneous T cell lymphoma each with a frequency of 2.8% each respectively.

In the present study Hypertension was associated with 9.5% of NHL cases. Among the hypertensive patients, Extranodal (56.5%) NHL was more commoner than Nodal (43.5%) NHL. DLBCL was the commonest subtype, followed by Follicular lymphoma with a frequency of 56.4% and 20.5% respectively. Other Extranodal lymphomas associated were Mycosis Fungoides, Angioimmunoblastic T cell lymphoma, Primary CNS lymphoma, PGL- Primary gastric lymphoma, Mucosa associated lymphoid tissue and Peripheral T cell lymphoma each with a frequency of 2.5% respectively.

Discussion

In the present study about 8.5% of NHL cases were associated with diabetes Mellitus. Similar to our study Alexander et al[12] showed 6% of NHL to be associated with diabetes, while, Bilora et al[13] reported association of diabetes only in 1.6% of NHL cases, which was low in comparison to our study (Table 1). Holly et al[14] in their study observed that the higher frequency of NHL in Diabetic patients was due to the use of cholesterol lowering drugs and non insulin drugs. He also states that DLBCL, FL and SLL were the most common subtypes associated with Diabetes Mellitus. However, Lin et al[15] states that NHL of T-cell origin, with extranodal involvement was common in Diabetes patients.

The increasing trends of NHL in China and Singapore also parallels with the increased cases of diabetes over the past four decades.[16,17] Studies from Taiwan[15] and japan[18] have reported a significant risk ratio of 1.88% and 1.58% respectively. Though the etiology of the increasing trend of NHL in Diabetics remains largely unknown. There are two school of thoughts, basically related to the treatment, one exogenous insulin which is potentially carcinogenic[19–21]. Two Oral antidiabetic drugs.[22]

Two Studies from Japan[7,23] and a study from Spain[22] have shown positive association between

Exogenous Insulin and NHL. Diabetes is associated with higher oxidative stress, inflammatory status, and immune dysfunction.[24,25–27] In Type 2 diabetes mellitus there is an established link between insulin resistance and inflammation. Although pro-inflammatory factors, such as tumor necrosis factor-a (TNF-a), promote insulin resistance [28,29] insulin also acts as a mediator for the inflammatory response.[30,31]

After binding to its receptor, insulin can activate either the metabolic pathway or the mitogenic pathway. In the presence of insulin resistance, a pathogenic characteristic of type 2 diabetes, the metabolic pathway is hampered and the mitogenic pathway is over activated, which may potentially lead to atherosclerosis and carcinogenesis. In addition, excessive insulin can also bind to the receptor of insulin-like growth factor- I, which will further trigger the mitogenic pathway. Patients receiving exogenous insulin in the presence of insulin resistance may be repetitively exposed to high levels of insulin, which may trigger the mitogenic and atherogenic pathways leading to hypertension, atherosclerosis, and cancer in susceptible patients.[32,33]

Insulin also regulates the expression of several hepatic proteins that are involved in inflammatory response.[30,22] The role of inflammation-mediating cytokines in lymphomagenesis is well accepted and is further confirmed by a recent large genetic association study.[34] Brody and Merlie[35] reported in 1970 that diabetic lymphocytes showed similar abnormalities in metabolism and DNA synthesis as lymphocytes in chronic lymphocytic leukemia.

A positive association between obesity and non-Hodgkin lymphoma has also been suggested.[36] Two recent meta-analyses by Renehan AG et al[37] and Larsson et al[38], reported significantly elevated non-Hodgkin lymphoma risk with increased body mass index. Larsson andWolk[38] further reported that the positive association for obesity was found only for diffuse large B-cell lymphoma but not for follicular lymphoma or small lymphocytic/chronic lymphocytic leukemia. However, Willett EV et al[39] showed risk only for DLBCL among severely obese individuals. As obesity is among the most important risk factors for type 2 diabetes mellitus it can indirectly contribute to the development of NHL.

Fortuny et al[22] reported increased risk for NHL with the use of oral antidiabetic agents.[40,41] Cerhan et al.[42] reported that risk increased as diabetes duration increased. Rapp et al.[43] examined the relations between fasting blood glucose and the incidence of several cancers. They found that elevated fasting blood glucose was positively associated with risk of non- Hodgkin lymphoma in men, whereas no association was found in women. More studies are needed to elucidate the lymphomagenic mechanism of type 2 diabetes mellitus.

However, two multinational studies, namely the European Prospective Investigation into Cancer and Nutrition study[44] and the Asia- Pacific Cohort Studies Collaboration[45] reported a lack of association between Diabetes Mellitus and NHL.

In the present study hypertension was associated with 9.5% of NHL cases. Hole DJ et al[10] also observed increased incidence of various cancer in hypertensive patients including lung, breast, skin, colon, stomach, bladder, rectum, prostate, pancrease, osephagus, ovary, cervix, kidney, melanoma, leukemia, myeloma and NHL. In their study they observed 3/136 (2.2%) cancer patients developed NHL who were on atenolol treatment.

Several studies raised the possibility that antihypertensive treatment may increase the rate of malignancy. A drug may increase the risk of malignancy either by being directly carcinogenic, by eliciting or accelerating other carcinogens, or by impeding defence mechanisms. Many clinical studies tried to determine whether antihypertensive drugs, in general, are carcinogenic.[46,47,48]

Bilora et al[13] have stated that the association of hypertension with NHL was due to autonomic changes in patients with lymphoma and may represent a paraneoplastic manifestation. Holly et al[14] in their study observed that use of drugs like Beta blockers, Calcium channel blockers, angiotensin-converting enzyme inhibitors, methyldopa, guanfacine, guanabenz, prazosin, and hydralazine were associated with higher frequency of NHL in hypertensive patients. He also stated that DLBCL, follicular lymphoma and SLL were the commonet subtypes of NHL in Hypertensive patients.

In another study by Peeters PH et al[49] they stated that hypertensive women have a higher incidence of mortality from lymphatic and hematopoietic cancers than men.[49]

Incidence of non- Hodgkin lymphoma continues to climb, elucidating the relation between Diabetes Mellitus and Hypertension. Further studies regarding mechanisms of lymphomagenesis, subtypes of NHL and specific drugs related to the development of NHL are needed in DM and HTN patients as they will provide means of NHL prevention.

Conclusion

Diabetes Mellitus and Hypertension are associated with development of NHL either directly or due to drugs used in the treatment. Nodal NHL are commoner than the extranodal NHL in Diabetic patients with Diffuse Large B Cell Lymphoma being the commonest subtype followed by Follicular lymphoma. Whereas, Extranodal NHL are commoner than Nodal NHL in Hypertensive patients with DLBCL being the commonest subtype, followed by Follicular lymphoma.

Further studies are required to identify the specific drugs involved and subtypes of NHL associated in the development of NHL especially in the Asian populations where prevalence of diabetes and Hypertension has increased in the recent years.

References

1. Baris D, Zahm SH. Epidemiology of lymphomas. Curr Opin Oncol 2000;12:383–394.
2. Tseng CH. Diabetes and non-Hodgkin's lymphoma: analyses of prevalence and annual incidence in 2005 using the National Health Insurance database in Taiwan Annals of Oncology 2012;23:153–158.
3. Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol 2005;84:1–12.
4. Ekstrom-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma—a review. Acta Oncol 2006;4:258–271.
5. Spronsen DJV, Janssen-Heijnen MLG, Breed WPM, Coebergh JWW. Prevalence of co-morbidity and its relationship to treatment among unselected patients with Hodgkin's disease and non-Hodgkin's lymphoma, 1993–1996 Ann Hematol 1999;78:315–319.
6. Winer N, Sowers JR: Epidemiology of diabetes. J Clin Pharmacol 2004. 44:397– 405.
7. Mitri J, Castillo J, Pittas AG. Diabetes and Risk of Non-Hodgkin's Lymphoma A meta-analysis of observational studies Diabetes Care 2008.31:2391–2397.
8. Frasca F, Pandini G, Sciacca L, Pezzino V, Squatrito S, Belfiore A, Vigneri R: The role of insulin receptors and IGF-I receptors in cancer and other diseases. Arch Physiol Biochem 2008. 114:23–37.
9. Lisker SA, Brody JI, Beizer LH: Abnormal carbohydrate metabolism in patients with malignant blood dyscrasias. Am J Med Sci 1966. 252:282–288.
10. Hole DJ, Hawthorne VM, Isles CG, McGhee SM, Robertson JW, Gillis CR, Jean AW, Lever AF. Incidence of and mortality from cancer in hypertensive patients. BMJ 1993. 306;6:609-612.
11. Grossman E, Messerli FH, Goldbourt U. Antihypertensive therapy and the risk of malignancies European Heart Journal 2001;22:1343–1352.
12. Alexander DD, Mink PJ, Adami HO et al. The non-Hodgkin lymphomas: A review of the epidemiologic literature. Int J Cancer 2009;120:1–39.
13. Bilora F, Veronese F, Zancan A et al. Autonomic dysfunction in Hodgkin and non-Hodgkin lymphoma. A paraneoplastic syndrome. Hematology Reports 2010; 2:e8.
14. Holly EA and Bracci PM. Population-based Study of Non-Hodgkin Lymphoma, Histology, and Medical History among Human Immunodeficiency Virus-negative Participants in San Francisco. Am J Epidemiol 2003;158:316–27.
15. Lin SY, Hsieh MS, Chen LS et al. Diabetes mellitus associated with the occurrence and prognosis of non-Hodgkin's lymphoma. Eur J Cancer Prev 2007;16:471–478.
16. Baris D, Zahm SH. Epidemiology of lymphomas. Curr Opin Oncol 2000;12:383–394.
17. Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non- Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol 2005;84:1–12.
18. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev 2007;16:83–89.
19. Hemkens LG, Grouven U, Bender R et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 2009;52:1732–1744.
20. Giovannucci E, Harlan DM, Archer MC et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685.
21. 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;29:254–258.
22. Fortuny J, Benavente Y, Bosch R, et al. Type 2 diabetes mellitus, its treatment and risk for lymphoma. Eur J Cancer 2005;41:1782–7.
23. Chao C, John H. Type 2 Diabetes Mellitus and Risk of Non-Hodgkin Lymphoma: A Systematic Review and Meta-Analysis American Journal of Epidemiology 2008;168:471–480.
24. Giovannucci E, Harlan DM, Archer MC et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685.
25. Kolb H, Mandrup-Poulsen T. The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. Diabetologia 2010;53:10–20.
26. van den Oever IA, Raterman HG, Nurmohamed MT, Simsek S. Endothelial dysfunction, inflammation, and apoptosis in diabetes mellitus. Mediators Inflamm2010;792393.
27. Vigneri P, Frasca F, Sciacca L et al. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123.
28. Hotamisligil GS, Peraldi P, Budavari A, et al. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNFalpha- and obesity-induced insulin resistance. Science 1996;271:665–8.
29. Borst SE. The role of TNF-alpha in insulin resistance. Endocrine 2004;23:177–82.
30. Campos SP, Baumann H. Insulin is a prominent modulator of the cytokine-stimulated expression of acute-phase plasma protein genes. Mol Cell Biol 1992;12:1789–97.
31. Fernandez-Real JM, Ricart W. Insulin resistance and inflammation in an evolutionary perspective: the contribution of cytokine genotype/phenotype to thriftiness. Diabetologia 1999;42:1367–74.
32. Giovannucci E, Harlan DM, Archer MC et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685.
33. Vigneri P, Frasca F, Sciacca L et al. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123.
34. Rothman N, Skibola CF, Wang SS, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the Inter Lymph Consortium. Lancet Oncol 2006;7:27–38.
35. Brody JI, Merlie K. Metabolic and biosynthetic features of lymphocytes from patients with diabetes mellitus: similarities to lymphocytes in chronic lymphocytic leukaemia. Br J Haematol 1970;19:193–201
36. Skibola CF. Obesity, diet and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2007;16:392–5.
37. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569–78.
38. Larsson SC, Wolk A. Obesity and risk of non-Hodgkin's lymphoma: a meta-analysis. Int J Cancer 2007;121:1564–70.
39. Willett EV, Morton LM, Hartge P, et al. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. Int J Cancer 2008;122:2062–70.

40. Evans JM, Donnelly LA, Emslie-Smith AM, et al. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330: 1304–5.
41. Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System.(Electronic article). BMC Med 2007;5:17.
42. Cerhan JR, Wallace RB, Folsom AR, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst 1997;89:314–18.
43. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. Diabetologia 2006;49:945–52.
44. Khan AE, Gallo V, Linseisen J et al. EPIC Group. Diabetes and the risk of non- Hodgkin's lymphoma and multiple myeloma in the European Prospective Investigation into Cancer and Nutrition. Haematologica 2008;93:842–850.
45. Lam EK, Batty GD, Huxley RR et al. on behalf of the Asia Pacific Cohort Studies Collaboration. Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. Ann Oncol 2011;22:730–738.
46. Williams RR, Feinleib M, Connor RJ, Stegens NL. Casecontrol study of antihypertensive and diuretic use by women with malignant and benign breast lesions detected in a mammography screening program. J Natl Cancer Inst 1978;61:327–35.
47. Rosenberg L, Rao RS, Palmer JR et al. Calcium channel blockers and the risk of cancer. JAMA 1998;279:1000–4.
48. Dyer AR, Stamler J, Berkson DM, Lindberg HA, Stevens E. High blood-pressure: a risk factor for cancer mortality? Lancet 1975;1:1051–6.
49. Peeters PH, van Noord PA, Hoes AW, Grobbee DE. Hypertension, antihypertensive drugs, and mortality from cancer among women. J Hypertens. 1998 Jul;16(7):941-7.