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# Diabetes and Cancer - Possible Role of Inherited Immunoglobulin

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## Introduction

Approximately 25% of the incoming diabetic patients in one medical practice have deficits in the total amounts of IgA, IgG and /or IgM. It is proposed that such deficiency may be significant in the strong association of diabetes with cancers. Furthermore, when type 1 diabetics with these deficiencies are treated with IV gamma globulin, they experience random episodes of severe hypoglycemia.

In 2001, a 67 year old, very well controlled type1 diabetic patient complained of progressively worsening sinusitis since age 3. He also had chronic diarrhea from infancy until age 4 that recurred at about age 63. He could not leave his home without taking large doses of potent anti-diarrheal agents.

Standard GI studies, including endoscopy, stool cultures and celiac antibodies were non-diagnostic. Since chronic inflammation of mucosa can suggest IgA deficiency, serum Immunofixation with quantification of immunoglobulins was performed. This disclosed a monoclonal IgM spike, low IgA, low IgG and elevated IgM. Follow-up studies of blood and bone marrow smears disclosed mild non-Hodgkin's Lymphoma (NHL). Subsequent genetic studies confirmed a diagnosis of Common Variable Immune Deficiency (CVID). Studies of his non-diabetic mother, sister and daughter also disclosed CVID in all three. His mother subsequently died of NHL and his sister also had a monoclonal spike of IgG, on immunofixation. She also suffered a rare malignancy – eosinophilic necrotizing xanthogranuloma [1].

The patient's lymphoma was promptly treated with Rituxan and he still receives frequent infusions of intravenous gamma globulin (IVIG), to control the severe sinusitis and severe diarrhea caused by his IgA and IgG deficiencies.

Not suspecting that CVID might be common amongst diabetics, I had not been screening my patients for this condition. In 2003 however, I began to check immunoglobulin levels in those patients (I only treat diabetics) who admitted to chronic infections on the initial history and also had low globulin levels on a routine metabolic profile. Noting an unexpected frequency of Immunoglobulin Deficiency (ID), I asked the immunology department of the Albert Einstein College of Medicine to analyze my data. They found that 19%, or 49 of my new patients had ID and published their findings [2] in 2011.

Since 2012, I have tested every new patient for total globulin; serum immunofixation, quantitative IgA, IgG and IgM levels, as well as visual study of blood Smears. During 2012, 8 out of 33 screened patients (25%) were positive for ID. Although routine screening was not performed in prior years, 80 of my patients are now known to have ID. The total number of new patients between 2003 and 2012 was 315.Of these, 25% have ID. Since many, if not most of my pre 2012 patients were not screened; additional asymptomatic patients with low Igs may be present in this population, possibly raising the ID fraction above 25%. A number of the positives also had monoclonal bands on serum immunofixation, but without detectable malignancies. Approximately 10% of these had histories of new malignancies including breast cancer, chronic lymphocytic leukemia, non-Hodgkin's lymphoma and tongue cancer (in a non-3Smoker). One patient developed MRSA after surgical removal of a growth on her back (cured by IVIG infusions). Two ID patients had longstanding, chronic pneumonia and are receiving chronic IVIG therapy. At least four of my patients and one sister are receiving chronic IVIG. All of my IVIG patients are type 1 diabetics, but about one third of the total with ID are type 2.

Although all of the IVIG patients had stable blood sugars before chronic IVIG, they all experienced frequent random severe hypoglycemic episodes as soon as treatment with IVIG began.

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Blood sugar drops have been as great as 100 mg/dl in one hour. These patients must check their blood sugars hourly during the day and every three hours at night in order to catch such episodes. The use of a continuous glucose monitoring device is recommended. It has been speculated by an immunologist who had previously observed this phenomenon in other type 1 diabetics, that IVIG fosters partial /temporary random beta cell recovery. Only one person is receiving chronic IVIG to treat a malignant disorder (eosinophilic necrobiotic xanthogranuloma) [1]. In this case the lesions originally resolved when her immunoglobulins were normalized but now dramatically recur at random. The association between diabetes and cancer has been the subject of much speculation [3] but little hard data. The observation that malignancies can be associated with Ig deficiencies dates back to 1959 [4]. Could it be that there really is an incidence of 25% or more ID amongst diabetics and could this be a significant factor in the elevated cancer incidence in this population?

I urge that investigators with access to suitably large diabetic populations secure blood levels of IgA, IgG, and IgM in order to generate more valid statistical data.

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