

Discontinuation of BCG Vaccination Precedes Significant Drop in Type 2 Diabetes in Japanese Children. Role of Inflammation and Cortisol Activity as a Cause of Type 2 Diabetes

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Abstract: BCG immunization was routinely given to elementary and junior high school students in Japan until it was abruptly discontinued after 2002. Data on the incidence of type 2 diabetes was analyzed to see if there was a change following discontinuation of BCG. The incidence of type 2 diabetes dropped by over 50% in children from Tokyo following discontinuation of BCG immunization, the relative risk reached 2.78 (95% confidence interval 1.03 - 7.480). This drop appears to be more significant given the epidemic of type 2 diabetes in children around the world. The increased secretion of cortisol following immunization is thought to result in metabolic syndrome and type 2 diabetes. Japanese children produce larger amounts of cortisol following immunization than White children. This increased production of cortisol may explain why Japanese children have a high risk of type 2 diabetes but low risk of type 1 diabetes compared to White children. The proposed mechanism may explain the epidemic of obesity which starts in children under 6 months of age.

Keywords: Type 1 diabetes, type 2 diabetes, BCG, vaccine, cortisol, inflammation.

RESEARCH DESIGN AND METHODS

BCG vaccine has been linked to an increased risk of type 1 diabetes [1]. BCG immunization was routinely given to Japanese elementary school children age 6 to 7 and junior high school children age 12 to 13 since prior to 1982. Immunization was discontinued at the end of 2002 [2]. BCG immunization rates were provided by The Research Institute of Tuberculosis, JATA. The incidence of type 2 diabetes in all elementary and all junior high school students in Tokyo Japan has been recorded since 1974 [3-5] and verified data has been published through 2004 [5]. Data on the incidence of type 2 diabetes was analyzed to determine if the incidence declined after discontinuation of BCG vaccine. Only incidence data of type 2 diabetes after 1982 was used because the age of BCG immunization changed in 1982 and this may explain the decreased incidence of diabetes prior to this time. Statistics were performed using Epiinfo 2000, CDC, Atlanta GA and a internet based Poisson calculator. A two stratification analysis was performed with one stratification using data from elementary school children and one stratification using data from junior high school students. Both Poisson and the more conservative Mantel-Haensel Weighted Relative Risk calculation was performed and Greenland/Robins Confidence Limits created. The P values with both methods were less than 0.05, with the later being less significant.

RESULTS

The results (Table 1) show that BCG immunization was associated with an relative risk of 2.78 ($1.03 < RR < 7.48$).

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CONCLUSIONS

The incidence of type 2 diabetes is increasing throughout the world in children [6] which makes the statistically significant drop in the incidence of type 2 diabetes in Tokyo so remarkable. Several theories have been proposed to explain the epidemic of type 2 diabetes. The obesity theory [7] holds that poor diet and lack of exercise are the cause for type 2 diabetes. A second theory postulates that increased inflammation [8] and the release of cortisol [9] are causing the epidemic of type 2 diabetes. The present data is consistent with inflammation as the cause of the type 2 diabetes epidemic in children.

The theory that poor diet and lack of exercise are causing the epidemic of type 2 diabetes in children has several short comings. The theory does not explain why obesity is increasing drastically in children under 6 month of age [10], who were never very active and don't eat fried foods or other junk food. It also does not explain the simultaneous epidemic of type 1 diabetes [11], which occurs primarily in thin patients. The cortisol theory [9, 12, 13] was based on the observation that small increases in cortisol activity are associated with metabolic disturbances including increased glucose levels, insulin resistance, increased blood pressure, obesity and hyperlipidemia [14]. Metabolic syndrome and related type 2 diabetes resemble mild Cushingoid Syndrome [15, 16]. However, the cause for the increased cortisol secretion had not been previously identified even though increased inflammation, which increases cortisol activity, had been identified [8, 9].

The decline in the incidence of type 2 diabetes in Japan can be explained by a recently proposed mechanism of action [17]. The proposed mechanism is that type 1 and type 2 diabetes are polar opposite aberrant responses to immunization and other immune stimulants. Immune stimulation with

Table 1. Rates of Type 2 Diabetes in BCG Vaccinated and Unvaccinated Children

	Year	Elementary School			Junior High School		
		Population	Cases Type 2 DM	Incidence Per 100,000	Population	Cases Type 2 DM	Incidence Per 100,000
BCG Vaccinated	1982	254,697	3		126,811	10	
	1983	241,793	2		125,427	8	
	1984	228,851	1		123,893	10	
	1985	214,655	3		125,404	10	
	1986	210,563	1		129,061	12	
	1987	213,617	0		131,667	7	
	1988	205,669	4		122,731	7	
	1989	204,940	1		114,777	5	
	1990	197,725	2		106,269	11	
	1991	210,832	0		108,625	4	
	1992	204,306	2		103,549	6	
	1993	198,283	2		96,766	10	
	1994	192,697	2		91,771	7	
	1995	186,653	2		88,079	8	
	1996	188,782	2		90,057	2	
	1997	178,134	2		85,794	7	
	1998	174,119	4		83,345	5	
	1999	170,539	3		79,893	4	
	2000	168,625	2		77,268	4	
	2001	172,505	1		76,950	3	
2002	169,706	1		73,227	4		
Totals		4,187,691	40	0.96	2,161,364	144	6.66
Not Vaccinated	2003-2004	307,213	1	0.33	122,690	3	2.45
				RR=2.93			RR=2.72
Two Strata Weighted Relative Risk: 2.78. 1.03<RR<7.48.							

vaccines causes some with low cortisol activity to develop an autoimmune disease including type 1 diabetes [18, 19]. It is known that decreases in cortisol following adrenalectomy leads to increased rates of type 1 diabetes in mice [20]. In others exposure to immune stimulation activates a neuroendocrine feedback loop to suppress the immune system through increased cortisol activity. Increased cortisol activity leads to type 2 diabetes and metabolic syndrome [9].

Vaccines have been shown to stimulate the immune system and can cause chronic inflammation [21, 22]. Vaccines have been shown to cause cortisol release [23-30]. This can be explained because vaccines cause the release of IL-6 [31-33] an cytokine that causes cortisol release [34-36]. Japanese have increased cortisol secretion following immunization

compared to Whites [37] and this explains why Japanese have higher rates of type 2 diabetes but lower rates of type 1 diabetes than Whites [4, 11, 38, 39].

This proposed mechanism explains several observations that the obesity theory does not. The vaccine-inflammation-cortisol mechanism explains why there is a simultaneous epidemic of type 1 and type 2 diabetes in children. Increased immunization can explain both epidemics. Type 1 diabetes has previously been linked to immunization [18, 19, 40]. BCG vaccine has been previously associated with an increased risk of type 1 diabetes [1] and is now associated with an increased risk of type 2 diabetes. The mechanism explains why the anthrax vaccine is associated with an increased risk of diabetes within 45 days post immunization [41], insulin

resistance, and greater than 45 days post immunization [41], destruction of islet cells and longer term changes in insulin resistance secondary to cortisol induced obesity. The mechanism explains why those with type 1 diabetes are skinny, lower cortisol activity [20], while type 2 diabetics are obese, higher cortisol activity [9]. It explains why obesity is increasing drastically in children under 6 month of age [10], vaccine induced cortisol activity. It also explains why diet and exercise have not been effective in preventing the epidemic of type 2 diabetes [7].

The observation that discontinuation of BCG immunization was followed by a drop in the incidence of type 2 diabetes needs additional follow up. The incidence of type 2 diabetes in Tokyo varies from year to year. Longer follow up would help better characterize the effect. Studies with other vaccines are also warranted.

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