Early Immune Disorders Induced By Childhood Obesity

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Introduction

Childhood obesity is increasing at epidemic proportions and is a massive public health concern (1). Obesity is associated with chronic inflammation and alteration in immune responses. This chronic low grade sterile or "cold" inflammation has been proposed to underpin the development of obesity related co-morbidites including insulin resistance, type 2 diabetes mellitus and cardiovascular disease (2). Obesity is also associated with increased risk of both auto-immune disorders (3) and cancer (4), although the cause has not yet been fully established. Immune system development is a continuous process throughout childhood with multiple maturation steps required to establish appropriate immune responses. Research determining the inflammatory environment and immune function in childhood obesity is essential to determine early mechanistic links between obesity and the development of complications, so as to permit prevention, early detection and intervention. A focussed review of immune disorders and related investigative work in childhood obesity will be described in this chapter.

Childhood obesity co-morbidities mediated through inflammation and immune dysregulation

There are multiple co-morbidities associated with childhood obesity. The increased incidence of metabolic, autoimmmune and inflammatory conditions in obese youth indicates how early the adverse effects of obesity on immune regulation can occur.

Metabolic conditions such as insulin resistance (IR) and Type-2 Diabetes Mellitus are steadily increasing in childhood obesity (5), with metabolic syndrome occurring in up to 50% of obese children in the United States . Macrophages have been proposed as the primary immune population in the development of IR. Adipose tissue macrophages (ATM) change to a pro-inflammatory state (M1) in obesity and subsequently secrete excessive pro-inflammatory cytokines which perpeutate hyperinsulinism (7). The risk of developing autoimmune Type 1 Diabetes Mellitus is also increased in children who are obese or have a higher body mass index (8), though the mechanism behind this is not fully understood.

Non-Alcoholic Fatty Liver Disease in children is becoming increasingly prevalent as a result of the obesity epidemic. There are reports of prevalence of NAFLD in up to 50-70 % of obese children (9). This can vary in presentation in children similar to adults, from fatty liver to steatohepatitis with risk of developing fibrosis and complications (10). Overexpression of pro-inflammatory cytokines and activated innate immune cells are central in the development of NAFLD. Activated Natural Killer T cells and Kupffer cells (liver specific macrophages) infiltrate into the hepatic tissue (11, 12) and result in increased levels of pro-inflammatory cytokines such as TNF a and Interferon g being secreted (13). These findings have also been described in a cohort of children, where NAFLD disease severity strongly correlated with hepatic tissue T cell infiltration (14).

Asthma is one of the most common chronic conditions of childhood. Obese children are more likely to develop asthma and to have more severe forms requiring increased health service utilization (15). Obesity

related asthma appears to be a distinct entity compared to typical asthma (16). Classic childhood asthma is atopic in nature and has a relative towards a Th2 phenotype, with secretion of cytokines IL-4, IL-4 and IL-13 and promotion of eosinophilia and IgE responses (16). Childhood obesity related asthma is characterized by a Th1 polarization, a predominantly pro-inflammatory mechanism that can cause autoimmune responses (17). In obesity related asthma there appears to be a paucity of local airway inflammation, instead the pathological process is mediated through systemic inflammation (18). Murine model studies demonstrate that part of immunological relationship between obesity and asthma may be inflammasome activation and the production of IL-17 cytokine from innate immune cells in the lung (19). Research to date points to obesity related asthma as being part of the systemic inflammation and immune dysregulation that characterizes the obese state.

Obesity is an immunosuppresssive state. There is increasing evidence that obesity can impair immune response to vaccines, with reduced responses to Hepatitis B vaccine reported in obese adults (20, 21) and to Tetanus vaccine in obese children (22) described. During the H1N1 Influenza Pandemic in 2009, it became apparent that obesity was a significant independent risk factor for influenza morbidity and mortality (23). Sub-optimal dendritic cell and CD8+ T cell immune responses to influenza in obesity have been shown . Influenza vaccination in obese children and adults demonstrated equivocal antibody response compared to their non- obese counterparts (25), but by 12 months this significantly diminished in obese individuals (26). Worldwide childhood vaccination schedules has been one of the most powerful tools in eradicating communicable disease morbidity and mortality. Childhood obesity may prove to be a significant threat to the protective effect of vaccinations in the future.

Multiple sclerosis is an immune mediated, demyelinating disorder of the central nervous system and is the most common cause of non-traumatic neurological disability in young and middle aged adults (27). Relationships between early life obesity and elevated risk of developing MS have been reported in studies (28-31). Multiple sclerosis, previously reported as rare in children, is becoming increasing recognized in paediatric populations (32), with risk particularly highest in obese adolescent girls. A proposed mechanism for the increased prevalence of this dehabilitating disorder in obesity is the chronic inflammatory state associated and the propensity towards Th1 polarization and development of autoreactive CD4+ cells (29).

Obesity is now recognized as a significant risk factor for risk of developing a malignancy (4). Twenty percent of adult cancer cases are attributed to being overweight or obese (4). In obese adult populations, increased incidences of multiple cancer types are described including post-menopausal breast, oesophageal, pancreatic, ovarian, renal cell carcinoma, endometrial and hemopoietic cancer types such as leukaemia and lymphoma (33). Children do not have a high cancer incidence overall, but there is evidence that being obese in childhood increases future risk. In obese children, there are reports of worse survival outcomes in hematological cancers such as Acute Lymphoblastic and Acute Myeloblastic Leukaemia (34-36). Larger body size in childhood and adolescence is associated with increased risk of non-Hodgkins lymphoma later in life (37). Research work is still underway to try to determine the exact mechanism by which obesity increases cancer risk. Studies in childhood are particularly important as they could elucidate mechanistic link prior to onset of other co-morbidities.

Inflammation in childhood obesity

Inflammation is a fundamental physiological process by which body tissues respond to irritation, infection or other injury. This can be acute, such as a localized trauma or injury, or chronic, such as what occurs in obesity or autoimmune disorders. In 1993 Hotamsigil and colleagues first described the relationship between adipose tissue expression of TNFa and insulin resistance in a murine model (38). Since then multiple adult obesity studies have re-affirmed that chronic inflammatory changes occur in obesity and that over-expression of these pro-inflammatory mediators play a fundamental role in the development of metabolic co-morbidities (2, 39). Adipose tissue macrophages play a distinct role in obesity-induced insulin-resistance and are major contributors to adipose tissue inflammation. In healthy subjects, macrophages have a regulatory M2 phenotype, producing anti-inflammatory cytokines including the archetypical regulatory cytokine – IL-10. In obesity, there is higher macrophage infiltration into adipose tissue and cells are polarized to the M1 inflammatory phenotype, producing pro-inflammatory cytokines including IL-1b (7). The majority of characterization of the inflammatory environment in obesity has been carried out in adults; we will discuss studies performed in childhood cohorts.

The first description of obesity-related inflammation in children was by Cook et al in 2000. They studied 699 children aged 10-11 years and reported that CRP levels were 270% higher in those in the top fifth of Ponderal index compared to those in the bottom fifth (40). These findings were replicated in 3512 children aged 8-16 years from the NHANES III survey, which reported that overweight boys and girls were 3.74 and 3.17 times more likely to have higher CRP compared with their normal weight counterparts (41). Multiple studies confirm that elevated CRP levels are present in obese childhood cohorts (42-44), even in children as young as 3 years of age (45). This association occurs across ethnic groups however non-caucasian obese children have a propensity towards higher CRP levels, particularly South East Asian, Hispanic American and Native Canadian groups. Multiple prospective studies in adults have shown CRP to be predictive of future cardiovascular disease, independent of obesity and so CRP has been proposed as a useful marker for the early diagnosis of metabolic syndrome and cardiovascular risk in obese children (46).

Human adipose tissue expresses pro-inflammatory cytokines such as interleukin-6 and TNF-a, potentially inducing low-grade systemic inflammation in individuals with excess body fat (2). Studies examining IL-6 production in obese compared to non-obese childhood populations describe varied results. Studies by Utsal et al (44) and Nagel et al (47) described elevated IL-6 levels in obese cohorts, whilst other studies did not report any difference (48, 49). Similarly, published reports describe variable TNF-a expression in obese childhood cohorts (41, 50). There are reports of other novel circulating inflammatory mediators being elevated in obese children. These include chemo attractant protein, chemerin in addition to IL-18, EGF and TNF-R2 (51, 52). IL-1b is a cytokine released from macrophages in response to activation by large, multiprotein complexes termed “inflammasomes”. IL-1b plays a key role in pancreatic cell toxicity, progression of inflammation and induction of insulin resistance, and thus is considered highly pathogenic in obesity-related metabolic disease (18). Antagonism of IL-1b is currently being targeted as a possible therapeutic strategy for T2DM (19). Elevated IL-1b levels both in serum (44) and post peripheral blood mononuclear cell stimulation (50) have been described in obese children. The detection of these pro-

inflammatory cytokines in obese children are concerning for the likely future trajectory of increased cardiovascular risk and onset of autoimmune disorders for these children.

Monocyte Chemoattractant Protein 1 is a key chemokine in the regulation of migration and infiltration of macrophages and monocytes (53). Their interaction with monocyte cells contribute to the pro-inflammatory state associated with obesity. Elevated MCP-1 levels are described in obese childhood cohorts (51, 54). As macrophages become pro-inflammatory, cleavage of the haptoglobin-hemoglobin receptor, CD163 becomes upregulated and is measurable as soluble-CD163 (sCD163). SCD163 is strongly associated with insulin resistance and in large adult studies correlated with risk of developing Type 2 Diabetes Mellitus (55). We have reported elevated CD163 levels in an obese childhood cohort, reflecting increased macrophage activation with polarization towards a pro-inflammatory phenotype (50). Elevation of these markers demonstrate that a pro-inflammatory skew of primary immune cells already occurs early on in obesity and this in turn adds to the pro-inflammatory environment that underpins obesity related co-morbidities.

Adiponectin is an insulin-sensitizing, anti-atherogenic adipokine with anti-inflammatory properties. Levels are decreased in obese children as young as 6 years old (43). Puberty has a significant effect on adiponectin levels and decreased levels observed with sexual maturation, with higher levels observed in girls compared to boys. A study by Mangge et al found a strong correlation between increased intima media thickness and reduced adiponectin levels in obese children when compared with lean controls (56), elucidating the importance of inflammatory mediators in the development of cardiovascular risk.

Immune cell alteration in childhood obesity

Monocytes are a vital innate immune cell population that can be categorized into subsets based on their expression of CD14 as a marker of activation (57). Increased monocyte concentration and the presence of activated status are both associated with hyperglycaemia and atherosclerosis in obese adults (58). Studies in obese children demonstrate both an increased CD14++ monocyte concentration (54) and an activated phenotype of the CD14++ monocyte subsets (51). Classic monocytes play a prominent role in obesity-associated disease due to their expression of MCP-1 receptors, CCR2. The expression of this receptor leads to their recruitment into adipose and vascular tissue by MCP-1. Within adipose tissue, monocytes further differentiate into inflammation producing macrophages (59). This further contributes to systemic inflammation and progression of obesity related disease.

Invariant Natural Killer T (iNKT) cells are a rare subset of innate T cells which bridge innate and adaptive immunity and may act as a link between the immune and metabolic systems (60). Murine and adult human studies have demonstrated that iNKT cells are highly enriched in adipose tissue but as adipose tissue expands in obesity, iNKT cells become depleted (61). Recent work in a murine model demonstrated that mice lacking iNKT cells had increased weight gain, insulin resistance and M1 macrophage polarization on a high fat diet. Adoptive transfer of iNKT cells led to decreased body fat and insulin sensitivity paired with a decrease in M1 macrophage frequency (60, 62). We quantified iNKT cell frequencies in obese compared to non-obese children and levels were significantly reduced in obese children. We demonstrated an inverse relationship between increased M1 macrophage polarization, by

using surrogate marker, sCD163 and decreased iNKT cell frequency in obese children (50). This provides further evidence that immune dysregulation that contributes to metabolic disturbance is already in progress in childhood.

Research work is still underway to try to determine the exact mechanism by which obesity increases cancer risk. Circulating cells of the innate and adaptive immune system play a critical role in tumor surveillance. Cytotoxic CD8+ T cells are considered to be the strongest effector cells of the adaptive immune system and play an integral role through cytokine production, transactivation and tumor lysis (63, 64). Natural Killer (NK) cells are innate effector cells that can induce the death of tumor cells, exercising their potent cytotoxic capacity without previous immunisation (63, 65). Reduced CD8+ T cells and NK cell populations have been previously described in obese adults (66, 67). A prospective study has demonstrated a relationship between the natural cytotoxicity of peripheral blood mononuclear cells and cancer risk showing that those with the lowest cytotoxic activity had the highest cancer risk (68). Key anti-tumour mechanisms have not yet been fully elucidated in childhood obesity, but given that there are significant immune cell changes at this early stage, further research is necessitated.

There is limited histological data on cellular infiltration of adipose tissue in obese children due to difficulty in obtaining tissue samples. A study performed by Sbarbati et al examining adipose depots from 19 obese children reports evidence of elementary lesions (69). These lesions are a microgranulomatous in nature and consist of macrophages, and to a lesser extent lymphocytes and granulocytes. These lesions are likely as a result of adipocyte fragility, with adipocyte degeneration leading to macrophage recruitment and fibrosis. This study provides insight that the inflammatory changes that characterize obesity related disease is precipitated with adipose tissue infiltration from early stage in obesity.

Conclusion

Childhood is a sentinel time for immune system development. Childhood obesity is now a significant public health problem. From a clinical perspective we have seen a surge in disorders that are immune in origin including asthma, diabetes mellitus and multiple sclerosis. Studies examining immune profile in obese children, although limited in number, demonstrate significant immune dysregulation from an early stage in obesity.

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Career Profile (Education and Employment)

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Associate Professor of Medicine, University College Dublin.
Head of the Obesity Research Group, Education and Research Centre, St Vincent's University Hospital, Dublin

Distinctions

1987. Auditor University College Dublin Medical Society.
1988. University College Dublin Medical Society President's Prize
1989. UCD and Mater Hospital Leonard Prize in Medicine
1993. Wellcome Trust Research Training Fellowship
1996. Patrick M Meenan UCDMGA Inaugural Research Medal
1998. Norman Plummer Prize for Postgraduate Clinical Research
1999. Imperial College School of Medicine Undergraduate Teacher of the Year
2006. Irish Endocrine Society O'Donovan Medal for group's research activity
2003-2008 & 2010 UCD Premier Award for Undergraduate Teaching Excellence

Peer Reviewed Funding

- Five Newman Scholarships Awards for post-doctoral scientists through UCD Foundations, 4 funded by Sanofi-Aventis: Obesity, immune dysfunction and chronic inflammation. 2006-2008 (Dr Lydia

Lynch), 2008 – 2010 (Dr Andrew Hogan), 2011-2013 (Dr Conor Woods), 2013-2015 (Dr Laura Tobin). One scholarship was funded by Ipsen; 2011-2013 (Dr G Gaoatswe). Value €95,000 each.

- Diabetes Federation of Ireland Health Research Board Project Grant 2006 – 2008. Adipocyte size and type 2 diabetes in obesity; a study of patients undergoing bariatric surgery. Value €181,000.
- Health Research Board Clinical Research Training Fellowship 2007-2009. Metabolically healthy obese and adipose tissue inflammation. Principal Supervisor. Applicant Dr Jean O'Connell. Value €183,000.
- Irish Heart Foundation Project Grant, 2009–2011. Smoking and the development of diabetes. Value €156,000
- National Children's Research Centre Obesity Consortium Project Grant 2011-2014. Chronic inflammation and innate immune cell dysregulation in obese children and adolescents. Value €234,756
- Paediatric SpR funded for 2 years to complete MD on the CRC-funded project, Value €120,000

Research and Mentoring

Thus far in my clinical research career I have established a consistent publication record in the fields of obesity and diabetes, with over 75 publications to date. In recent times my research group has published articles on the immune effects that the above conditions elicit.

I have now supervised 4 clinicians (Dr's Khatib, Abusnana, Cawood and O'Connell) to completion of their PhD and 1 to completion of his MD (Dr Bashir). I have 4 clinicians registered for their PhD (Dr's Woods, Ahern, Gaoawste and Carolan) and 2 for an MD (Dr's Kattak & Armin). Dr Eirin Carolan and her successor Dr Meenal Mavinkurve, have undertaken research paediatric obesity research projects in collaboration with Dr Declan Cody of Our Lady's Children's Hospital. With Dr Brian Kirby, I have co-supervised a dermatologist (Dr Anne Marie Tobin) for her PhD and with Prof Walter Mc Nicholas, I am co-supervising Dr Brian Kent for his PhD. Both attended and presented their experimental/trial plans at our weekly meeting. I have supervised two dietitians in our unit to completion of their Masters (Alison Quinn and Lorraine Cooney). I am especially pleased that another of our dietitians, Cathy Breen, has taken time out to undertake a PhD. She has completed her PhD transfer and is in the final year of her studies and had 3 publications based on her PhD project. At present, I have 3 postdoctoral scientists (Dr Andrew Hogan, Dr Michelle Corrigan and Dr Laura Tobin). My current students are on track for successful completion of their PhD/MDs, with excellent opportunity for publication.

Publications

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3. Carolan E, Hogan AE, Corrigan M, Gaotswe G, O'Connell J, Foley N, O'Neill LA, Cody D, O'Shea D. The impact of childhood obesity on inflammation, innate immune cell frequency and metabolic

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4. Hogan AE, Gaoatswe G, Lynch L, Corrigan MA, Woods C, O'Connell J, O'Shea D.Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus.Diabetologia. 2013 Dec 21. [Epub ahead of print]PMID: 24362727 [PubMed - as supplied by publisher]
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12. Sahebally SM, Burke JP, O'Shea D, Geoghegan J.The effect of gastric band slippage on patient body mass index and quality of life. Obes Surg. 2012 May;22(5):773-6.
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