Introduction

Over the last 30 years, many publications have suggested an association between Down syndrome and thyroid disorders, and showed altered levels of abnormal thyroxine (T4) and thyroid stimulating hormone (TSH) levels. Such changes may be present along with other hormonal and biochemical disturbances ***(Hestnes et al., 2005).***

Thyroid dysfunction in children with Down syndrome (DS) can occur as early as birth. With the age, there is risk for thyroid autoimmunity manifested as autoimmune hypo-thyroidism or Graves's disease increases. The optimal timing and method for thyroid screening in children with DS remains controversial. The American Academy of Pediatrics recommends annual screening in this population ***(Graber et al., 2012).***

The etiology of acquired hypothyroidism remains uncertain, although it is probably secondary to auto-immune thyroiditis ***(Gilchrist 2004).*** It is far more difficult to diagnose thyroid deficiency in children with Down's syndrome than in the general population. Some classic features of poor thyroid function like tiredness, overweight and general sluggishness have already been mentioned in Down syndrome. In addition the person may feel the cold, have a tendency to constipation, dry skin, sparse hair, and a rather hoarse voice ***(Pitt et al., 2002).***

The increase in the prevalence of hormonal abnormalities is also associated with increase in the prevalence of autoimmune thyroiditis ***(Pascanu et al., 2009).***

Subclinical hypothyroidism is particularly common in children with Down syndrome, with prevalence ranging from 25.3 % to 60 % ***(Tuysuz et al., 2001).***

Thyroid hormone acts on the heart and peripheral vasculature in multiple ways. Triiodothyronine, the bioactive hormone, is known to affect tissue oxygen consumption, vascular resistance, blood volume, cardiac contractility, and heart rate ***(Klein et al., 2001).***

Patients with overt hypothyroidism have bradycardia, decreased ventricular filling, and decreased cardiac contractility, which lead to decreased cardiac output ***(Crowley et al., 1977).*** Subclinical hypothyroidism may have similar but more subtle effects on cardiac function ***(Biondi et al, 2002).***

On the other hand, in overt hyperthyroidism, increased cardiac contractility and altered left ventricular (LV) loading result in a hyperdynamic state, with high cardiac output at rest and a suboptimal response to exertion ***(Osman et la, 2002).***

Aim of the Work

The aim of this work is to evaluate cardiac functions in relation to the thy roid profile in patients with Down syndrome

Down Syndrome

Definition and incidence of DS:

Down syndrome (DS) is a complex set of pathologies caused by an extra copy of human chromosome 21. DS occurs in about 1 in 750 live births and is the most frequent cause of learning difficulties. Although the underlying genetic cause is the same in most individuals with DS, the penetrance of the resulting pathologies is varied **(Antonarakis et al., 2004).**

DS occurs in all races and economic levels, though older women have an increased chance of having a child with Down syndrome. A 35 year old woman has about a one in 350 chance of conceiving a child with Down syndrome, and this chance increases gradually to 1 in 100 by age 40. At age 45 the incidence becomes approximately 1 in 30. The age of the mother does not seem to be linked to the risk of translocation ***(Harvey et al, 2005).***

Table (1): The relation between maternal age and incidence of DS.

Maternal Age	Incidence of Down syndrome	Maternal Age	Incidence of Down syndrome	Maternal Age	Incidence of Down syndrome
20	1 in 2,000	30	1 in 900	40	1 in 100
21	1 in 1,700	31	1 in 800	41	1 in 80
22	1 in 1,500	32	1 in 720	42	1 in 70
23	1 in 1,400	33	1 in 600	43	1 in 50
24	1 in 1,300	34	1 in 450	44	1 in 40
25	1 in 1,200	35	1 in 350	45	1 in 30
26	1 in 1,100	36	1 in 300	46	1 in 25
27	1 in 1,050	37	1 in 250	47	1 in 20
28	1 in 1,000	38	1 in 200	48	1 in 15
29	1 in 950	39	1 in 150	49	1 in 10

(*McGuire *et al, 2010)

1959, the French physician Jerome Lejeune identified Down syndrome as a chromosomal condition. Instead of the usual 46 chromosomes present in each cell, Lejeune observed 47 in the cells of individuals with Down syndrome. It was later determined that an extra partial or whole copy of chromosome 21 results in the characteristics associated with Down syndrome. In the year 2000, an international team of scientists successfully identified and catalogued each of the approximately 329 genes on chromosome 21. This accomplishment opened the door to great advances in Down syndrome research **(Malt et al., 2013).**

Incidence of DS in Egypt:

In Egypt, the incidence of DS has been reported to be 1 per 1000 births ***(Abdel-Fattah S,1991).***

DS in United States and Europe:

One in every 691 babies in the United States is born with DS, making down syndrome the most common genetic condition, Approximately 400, 000 Americans have Down syndrome and about 6.000 babies with Down syndrome are born in the United States each year **(Roizen *et al.*, 2005).**

In adulthood about 20% in the united states do paid work in some capacity with many requiring a sheltered work environment support in financial and legal matters is often needed, life expectancy is around 50 to 60 years in the developed world with proper health care **(RichardUrbano *et al.*, 2010).**

Between 5 and 15% of children With Down syndrome in Europe attend regular school. Some graduate from high- school, however, most do not. of those with intellectual disabilities in the United States who attended high school about 40% graduated. Many learn to read and write and some are able to do paid work. In adulthood about 20% in the United States do paid

work in some capacity. In Europe, however, less than 1% have regular jobs Many are able to live semi-independently but they often require help with financial, medical, and legal matters. Those with mosaic Down syndrome usually have better outcomes **(Morris et al., 2002).**

Clinical picture of DS

Characteristic facies is one of the few phenotypes seen in all individuals with DS, and is the result of an underlying craniofacial dysmorphology, which includes reduced skull size, flattened occiput , brachycephaly , small mid face and reduced size of the maxilla and the mandible **(Richtsmeier et al., 2002).**

Common physical signs include: decreased muscle tone at birth, excess skin at the nape of the neck , flattened nose , separated joints between the bones of the skull (sutures), simian crease in the palm of the hand , small ears , small mouth ,upward slanting eyes ,brachydactyly(short broad hand), clinodactyly of the little finger , white spots on the colored part of the eye (Brushfield spots). **(Bacino,et al., 2011).**

Fig. (1): 8-year-old boy with Down syndrome ***(Cauldwell et al., 2006).***

Altered immune system function, muscular hypotonia, and premature ageing contribute to health problems .DS patients are also susceptible to infections, particularly of the respiratory and the gastrointestinal tract **(Malt et al., 2013).**

Neonates with DS present with muscle hypotonia and many individuals with DS demonstrate some form of motor impairment, often described as clumsiness or deficits in fine motor control **(Moldrich et al., 2007).**

A total of 40–61% of individuals with DS present with congenital heart defects (CHDs), a major cause of high morbidity or infant mortality in individuals with DS. The most common heart malformation in DS is the atrioventricular septal defect (AVSD), which is considered a hallmark of DS: The

incidence of AVSD is 1000-fold increased in individuals with DS compared with the non-DS population (**Vis et al., 2009**).

Approximately half of the children with Down syndrome have congenital heart disease and associated early onset of pulmonary hypertension. An echocardiogram may be recommended to identify any congenital heart disease. If the heart defects have been identified before the onset of pulmonary hypertension, surgery may provide favorable results **(William *et al.*, 2012).**

Recent studies indicate that 66 percent to 89 percent of children with Down syndrome have a hearing loss of greater than 15 to 20 decibels in at least one ear, due to the fact that the external ear and the bones of the middle and inner ear may develop differently in children with the syndrome. Many hearing problems can be corrected. But, because of the high prevalence of hearing loss in children with Down syndrome, an objective measure should be taken to establish hearing status. Hearing problems, like eye problems, may be present early in life **(Rodman and Pine, 2012).**

Compared with the non-DS population, individuals with DS have an 18-fold increased risk of developing leukaemia . In particular, DS is associated with a 500-fold increased risk of acute megakaryoblastic leukaemia (AMKL). there is a

approximately 12-fold increased risk of acute lymphoblastic leukaemia in the age group of 5-30 years that rises to approximately 40-fold in children younger than 5 years **(Hasle et al., 2000).**

Congenital gut disorders have an increased incidence in DS. Patients with DS constitute ~12% of all cases of Hirschprung's disease, and duodenal stenosis and imperforate anus are 260 and 33 times more likely to occur in DS, respectively **(Korbel et al., 2009).**

Instability of the atlanto-axial joint occurs in approximately 20% and may lead to spinal cord injury in 1-2% Hip dislocations may occur without trauma in up to a third of people with Down syndrome **(Szabo and Liz, 2013).**

Growth in height is slower resulting in adults who tend to have short stature, the average height for men is 154 cm (5 feet 1inch) and for women is 142 cm (4 feet 8 inches). Individuals with Down syndrome are at increased risk for obesity as they age **(Hickey et al., 2012).**

Most individuals with Down syndrome have mild (IQ:50-70) or moderate (IQ: 35-50) intellectual disability with some cases having severe (IQ: 20-35) difficulties. Those with / mosaic Down syndrome typically have IQ scores 10-30 points higher **(Sankar et al., 2008).**

Compared to the general population, individuals with Down syndrome have a twelve fold higher mortality rate from infectious diseases if these infections are left untreated and unmonitored. These infections are due to problems in their immune systems, usually the T cell and antibody-mediated immunity functions that fight off infections. Children with Down syndrome are also more likely to develop: Chronic respiratory infections middle ear infections (otitis media) and recurrent tonsillitis. In addition, there is a 62-fold higher incidence of pneumonia in children with Down syndrome than in the general population **(Richard *et al.*, 2010).**

The molecular mechanisms leading to the immune defects observed in DS individuals and the contribution of immunological abnormalities to the increased risk of infections require further investigation. Addressing immunological and non-immunological factors involved in the pathogenesis of infectious diseases may reduce the susceptibility to infections in DS subjects **(Ram et al., 2011).**

Table (2): The prevelance of some common features of DS

Characteristics	Percentage	Characteristics	Percentage
Mental impairment	99%	Abnormal teeth	60%
Stunted growth	90%	Slanted eyes	60
Umbilical hernia	90%	Shortened hands	60%
Increased skin back of neck	80%	Short neck	60%
Low muscle tone	80%	Obstructive sleep apnea	60%
Narrow roof of mouth	76%	Bent fifth finger tip	57%
Flat head	75%	Brushfield spots in the iris	56%
Flexible ligaments	75%	Single transverse palmar crease	53%
Large tongue	75%	Protruding tongue	47%
Abnormal outer ears	70%	Congenital heart disease	40%
Flattened nose	68%	Strabismus	~35%
Separation of 1st and 2nd toes	68%	Undescended testicles	20%

(Hammer et al., 2010)

Speech disorders in Down syndrome (DS) includes voice, speech sounds, fluency and prosody, and intelligibility. Stuttering and/or cluttering occur in DS at rates of 10%-45%, compared with about1% in the general population **(Kent et al, 2013).**

As children with DS age, their risk for thyroid autoimmunity manifested as autoimmune hypothyroidism or Graves disease increases. The optimal timing and method for thyroid screening in children with DS remains controversial. The

American Academy of Pediatrics recommends annual screening in this population . Consensus is needed to establish working definitions of euthyroidism and mild hypothyroidism in all infants, but especially in those with DS **(Graber et al., 2012)**

Genes that are over expressed on chromosome 21 are associated with oxidative stress and neuronal apoptosis. The lack of balance in the metabolism of free radicals generated during processes related to oxidative stress may have a direct role in producing the neuropathology of DS including the tendency to Alzheimer disease (AD). Mitochondria are often a target for oxidative stress and are considered to be a trigger for the onset of the AD process in DS. Biomarkers for oxidative stress have been described in DS and in AD in the general population. However, intervention trials using standard antioxidant supplements or diets have failed to produce uniform therapeutic effect **(Lott et al., 2012).**

Adolescents with DS undergo the same hormonal changes during puberty as typically developing children. Girls with Down syndrome have regular menstrual periods and should receive instructions on hygiene. Although women with Down syndrome are not very fertile, they can become pregnant. Men with Down syndrome have low sperm count, but in some cases have fathered children. Proper education regarding sexual development and contraception is very important **(Mohan et al., 2009).**

DS is characterized by the early onset of the neuro pathological features of Alzheimer's disease (AD) and the eventual onset of dementia. A strong candidate for a dosage-sensitive gene contributing to this phenotype is amyloid precursor protein (*APP)*, because proteolysis of APP generates amyloid-β (Aβ), the main constituent of amyloid plaques in AD brains, and mutations or duplications of *APP* have been associated with early onset AD.**(McNaughton et al., 2010).**

Diagnosis of DS:

Amniocentesis for karyotyping of fetal cells, fluorescent in-situ hybridisation (FISH) and karyotyping, are definitive methods of making the diagnosis antenatally and postnatally ***(Mittal et al., 2009).***

Prenatal screening of DS:

DS is the most common cause of mental retardation and has an incidence of between 1:600 and 1:800 pregnancies. It is the condition for which prenatal diagnosis is requested the most developed countries have adopted a screening program based around maternal plasma/serum testing and ultrasound ***(Avent et al., 2013).***

Prenatal screening for DS is performed by risk calculation based on biochemical and biometric parameters, In this way, approximately 75-85% of all DS cases can be detected ***(Koster et al., 2010).***

Advances have been made recently to eliminate invasive testing for genetic diagnosis of this condition based on the analysis of free fetal DNA in maternal plasma.. Screening based on assessment of various biomarkers present in maternal plasma represents a front-line test to assess the risk of the mother carrying an aneuploid fetus. Recent comparative proteomics techniques have resulted in studies that have assessed maternal plasma from mothers carrying normal and trisomy 21 fetuses and various gestational ages. Over 100 biomarker candidates have been described, but little consensus has emerged. This may be due to a number of compounded factors, but interesting to note that other neurological disorders have overlapping biomarkers ***(Avent et al., 2013).***

Nuchal translucency has proven to be an effective and cost-effective screening test that, when combined with serum markers (hCG and pregnancy-associated plasma protein [PAPP-A]) in the first and/or second trimester, broadens the diagnostic possibilities and improves the diagnostic capabilities of current prenatal DS screening methods ***(Fuch et al., 2005).***

A way to improve detection rates is to search for new screening markers. Since the majority of biomarkers used in current DS screening are predominantly produced by the placenta, and the presence of an extra chromosome (as in DS) complicates placental development and function, it is plausible to assume that new potential screening markers may also