The relationship between insulin exposure and breast cancer nursing essay

Health & Medicine, Nursing

Introduction

Breast Cancer

Cancer Research UK states that cancer is the cause of more than a quarter of all deaths in the UK with breast cancer being the most common type suffered in women. According to the Office for National Statistics, between 2008 and 2010, an average of just under 49, 000 women were being diagnosed with breast cancer each year. Furthermore, they found that an average of 11, 757 females lose their lives each year from this condition, which is around 25 deaths per 100, 000 women or around 32 every day. There has been a huge rise in the incidence of females breast cancer in the UK in the past 40 years, with an increase of almost 70% since the mid-1970s. Breast cancer is not only diagnosed in females, males can also suffer from it but the incidence in men is much lower with only around 400 men being diagnosed in 2010. There are a wide range of risk factors that influence the development of breast cancer; these include older age, family history, breast cancer genes, hormones, hormone replacement therapy, contraception, having children early in life, ethnicity, previous breast cancer, alcohol, smoking and being overweight after menopause. Possible factors that increase the risk include stress, termination of pregnancy and an injury to the breast. Furthermore, diabetes is also listed by Cancer Research UK as a definite breast cancer risk, but there is still no definite answer as to why.

Diabetes

Diabetes is a lifelong condition that comes in two types (1 and 2) and can result in hyperglycaemia (raised blood glucose levels). According to the NHS,

in the UK there are approximately 2. 9 million sufferers of the condition with type 2 accounting for approximately 90% of these. Type 2 diabetes can be a result of 3 different mechanisms, one being absolute insulin deficiency where there is a decrease in the secretion of insulin from the pancreas. Second is relative insulin deficiency where sufficient insulin secretion is absent due to factors such as obesity, as fat cells become active. Another factor is resistance to the insulin that is circulating the blood, which is why it is seen that most sufferers of type 2 diabetes are also obese. The final mechanism, insulin resistance, is the most common and is where an insulin utilisation defect occurs. This defect can be influenced by factors like genetics, ethnicity, age, diet, obesity and exercise and to treat it a patient requires more insulin to store the glucose gained from food, through the lock and key mechanism. Type 2 diabetes is normally treated with oral treatments such as metformin, sulphonylureas or thiazolidinediones, however if a patient with diabetes is not controlled with these drugs, it is possible for the patient to be prescribed insulin. In type 2 diabetics, approximately 27% use insulin therapy.

Insulin

Insulin has been used since the 1920s and is mainly used in patients with type 1 diabetes because of their inability to produce it. However, as explained above under certain circumstances it can be prescribed for a sufferer of type 2 diabetes. Insulin is a hormone produced in the islets of Langerhans in the pancreas by Beta cells to help our body store the glucose we consume as energy. There are many types of insulin that can differ with

onset time, peak time or duration of action. There are rapid-acting insulin analogues (novorapid) which has the fastest onset time. Also short acting insulins (human actarapid), intermediate acting insulins (isophane NPH), long acting analogues (insulin glargine) and long acting insulins (protamine zinc). The aim when treating a patient with insulin is to try and keep the insulin levels in the body as close to that of a non-diabetic as possible while taking into account the risk of hypoglycaemia (low blood sugar level) which can occur if insulin levels are too high. Patients tend to be given one of two regimens, biphasic or basal bolus. The biphasic regimen is a mixture of short and intermediate acting insulins taken twice daily, once in the morning and once at teatime. Basal bolus is to take one intermediate or long acting in the evening and a dose of a short acting insulin before meals (normally 3 doses). The purpose of this protocol is to look at the relationship between insulin exposure and breast cancer in type 2 diabetics. From these statistics we can see that type 2 diabetes is a more common type of diabetes, and breast cancer is a more common cancer in women. To understand the link between the exposure to insulin and its relationship with breast cancer, we must understand the proposed mechanism of action that links the two together.

Mechanism of Action

Type 2 diabetes is associated with insulin resistance, increased inflammatory markers and increased reactive oxygen species which all relate to a high insulin level. Insulin resistance in particular relates to hyperinsulinemia, where there are excess levels of insulin circulating in the blood relative to the level of glucose. Due to the strong anabolic effect of insulin, and because

it is at a high level, proliferative tissue abnormalities are induced, which results in the stimulation of DNA synthesis and cell proliferation. Another process that can result in this is the cross-activation of the insulin-like growth factor (IGF) receptor family. IGFs are proteins that have a very similar protein sequence to that of insulin and come in two types, IGF-1 and IGF-2. IGFs regulate cell growth, cell differentiation, cell apoptosis and cell transformation in different tissues including breast tissue. IGF-1 is secreted due to stimulation by a growth hormone and is important for the maintenance of normal physiology in the body and can be important in breast cancer too as it has been reported that it stimulates the growth of breast cancer cells. Both IGF-1 and insulin activate the tyrosine kinase growth receptor pathway for insulin, IGF-1 and a hybrid of the two receptors. These three including the hybrid are all overexpressed in breast cancer cells. Furthermore, high insulin levels activate insulin receptors as expected. When these receptors are activated, they will phosphorylate intracellular proteins. This phosphorylation leads to the activation of extracellular signal regulated kinase cascade, which is one of the mitogen-activating protein kinase (MAPK) pathways. This pathway increases mitogenesis and can increase the risk of breast cancer. The two theories above are shown below in two separate flow chartsType 2 diabetesInsulin resistanceHigh insulin levels because of hyperinsulinemiaInduction of proliferative tissue abnormalitiesStimulation of DNA synthesis and cell proliferationTheory 1. Theory 2. Cross activation of IGF receptor familyIGF-1 and insulin activate the tyrosine kinase growth pathwayInsulin receptor activatedPhosphorylation of intracellular proteinsActivation of extracellular signal regulated kinase cascade (MAPK

pathway)Increase in mitogenesisHigh insulin level (can also cause insulin receptor activation)

Type 2 Diabetes and Breast Cancer

The proposed link between type 2 diabetes and breast cancer has been studied on many occasions. A Nurses' Health Study from 2003 came to the conclusion that women with type 2 diabetes have a slight but significantly greater risk of developing breast cancer than women who do not have diabetes. This study had a large sample size of 116, 488 females aged from 30 to 55 years however the limitation in terms of this protocol is that it did not include any analysis on whether the patients used insulin. Furthermore, a cohort study using the UK General Practice Research Database found that diabetes was associated with a 29% increase in risk of breast cancer (95% CI: 1. 16-1. 44). However, the problem with this study was that the relationship was markedly reduced when age, region and BMI were taken into account (HR: 1. 12; 95% CI: 0. 98-1. 29). With these being associated with a differing risk of breast cancer, you question the validity of the results. This study also showed that there is a 49% increase in mortality in women with breast cancer who had diabetes previously, when compared to women with breast cancer without diabetes. This analysis of mortality however, gave unreliable results because of the small limited number of studies available with the data and a short follow up period of only 1 year in some. These two studies above show the risk of type 2 diabetes with breast cancer, but do not evaluate how the types of treatments can influence it.

Insulin and Breast cancer

When looking at insulin and breast cancer there is two links that have been proposed. One of these is whether the use of insulin increases the risk of women being diagnosed with breast cancer. Secondly, do insulin levels increase the risk of mortality in women who have previously been diagnosed with breast cancer? A cohort study was carried out using the General Practice Research Database (GPRD) from the UK to " determine the long term effects of insulin glargine on the risk of breast cancer". They extracted patients from the database (containing 9. 9 million people) who were female, had type 2 diabetes and had at least one prescription for any type of insulin between 01/09/2002 and 31/12/2006. The fact that the study was concentrating on only type 2 diabetes and specifically breast cancer as the outcome is a huge advantage to this protocol. Each patient who had been exposed to insulin glargine was matched with a reference patient who used another type of insulin. They had well thought exclusion criteria for example women with a history of breast cancer. This study also had a good sample size of 15, 227 women, with 4, 579 in the insulin glargine cohort and 10, 648 in the other insulin cohort. The study also had a long follow up period of 8 years and after this follow up, 246 of the whole sample had developed breast cancer. A limitation of the study could have been that the users of insulin glargine were seen to be leaner, have less well controlled diabetes and used more oral anti-diabetic treatments. This could have affected the outcome as treatments such as hHormone replacement therapy (HRT) are reported to possibly increase the risks of cancers. A further limitation of this study was that the dose of insulin was not taken into account so the investigators were

not to know if the women who had developed breast cancer were taking the insulin at a higher dose ? frequency than others which could have improved understanding further. There is a gap in knowledge here and could be incentive for a study in the future to determine whether a high level of insulin used can increase the risk of breast cancer when compared to a lower level use. The main conclusion we gain from this cohort study was that insulin glargine use is not associated with an increased risk of breast cancer when compared to users of other insulins (HR 1. 0; 95% CI 0. 7-1. 4). However they did find that after more than 5 years of use of glargine, a trend towards an increase in risk was showing except in first time users. This is shown below in Figure 1 extracted from the paper. Figure 1. title here with a referenceThe solid curve represents the hazard ratio of the incidence of breast cancer. Dotted lines represent 95% confidence limits against the number of years since glargine use was initiated compared to time frame for use of other insulins. Furthermore, the way breast cancer was identified was using the first diagnosis only. Even though early diagnosis in breast cancer mostly results in an improved outcome, some cases could have been misdiagnosed which was not taken into account here. A further gap in knowledge is identified because as mentioned in the introduction there are many types of insulin and some have very limited data available for example insulin detemir and these studies justify the need for it. In conclusion, when looking at the effect of insulin on breast cancer in type 2 diabetics it would be more definitive to use a prospective study however there would be problems with its practicality and ethics due to the controversy surrounding

certain insulins that are more effective in reducing morbidity and mortality in diabetes.

Summary of literature

From the literature search, studies were found that investigated the link between type 2 diabetes and breast cancer, and one that studied the effects of certain insulins against others in terms of breast cancer risk. However there has not been a study as of yet evaluating whether exposure to insulin specifically in type 2 diabetics, can cause an effect on the risk of breast cancer especially. Therefore the gap in knowledge is present here which is where this protocol comes in.

Hypothesis

After studying the theories of the mechanisms of action of how insulin may cause cancer and in particular breast cancer, and looking at the literature above, it is possible to come up with a hypothesis. I think that insulin exposure in type 2 diabetes will cause an increase in the risk of developing breast cancer in women. Dose-response relationshipType of insulin used. Good.