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Editorial

Winners Vs. Losers: Are the Patients the Real Winners in this Game?
Juan S. Barajas-Gamboa

Research Articles

Anemia and Hemoglobin A1c level: Is there a case for redefining reference ranges and therapeutic goals?
Segun Adeoye, Sherly Abraham, Irina Erlikh, Sylvester Sarfraz, Tomas Borda and Lap Yeung.

Frequency and severity of depression among mothers of children with cancer: Results from a teaching hospital in Karachi, Pakistan
Mariam Ghufran, Marie Andrades and Kashmira Nanji

Review Articles

Physical activity after cancer: An evidence review of the international literature
Robert James Thomas, Mea Holm and Ali Al-Adhami

Case Reports/Series

An unusual reaction to IV pethidine - A Case Report
Prakash Krishnan and Asquad Sultan

An aggressive follicular variant of papillary thyroid carcinoma with unusual metastases - A case report and review of literature
Isaac Sachmechi, Rachelle N Bitton, Susan Sanelli-Russo and Supat Thongpooswan

Patellar fracture fixation: An unreported complication occurring directly attributable to tension band fixation of the patella.
Peter Alexander Gilmer Torrie, James, Smith and Micheal Kelly.

Self-induced burn injury from thermal footbath in patients with diabetes neuropathy—a common mishap in Asian culture
Huai Heng Loh and Florence Tan

Medical Images

Photo Quiz: Palatal swelling with pain
Segun Adeoye, Sylvester Sarfraz and Kiranmayi Korimerla

Miscellaneous

“Of the depression” - A Poem by Dr Javed Latoo
Javed Latoo
Winners Vs. Losers: Are the Patients the Real Winners in this Game?

Juan S. Barajas-Gamboa

It cannot be denied that healthcare services have become an attractive business for any party involved, whether it be government, insurance companies, hospitals and doctors, to look out for their own interest and leave aside the real priority of this system – the patients’ healthcare and welfare.¹

Recent proposed changes in the health system (i.e. healthcare reform) have commanded the attention of all people involved. If nothing else, it has provided an avenue in which each detail can be scrutinized and assessed. And, ultimately, it can be used to optimize the balance of clinical outcomes with resource requirements.

As expected, each guild has its own theories and proposals for improving the delivery of care. However, coming to a consensus will be a difficult task given the economic interests at stake. It should be obvious that the most important guild affected by the changes is the guild formed by patients.²

From the physician’s point of view, achieving optimal patient care has become more difficult. In part, this is due to how the government has chosen to assess and improve the delivery of healthcare services, which is by implementing patient surveys to assess the quality of care and level of satisfaction. Basically, the government has hired private companies to prepare and distribute these assessments. Based on the results of these surveys, the government will allocate various economic resources. As a strategy to face these measures, hospitals have established annual incentive plans to motivate doctors to get good scores in patient satisfaction surveys, including offering higher salaries and compensations.² ³

This impasse pushes the system to operate in an inappropriate manner. For example, hospitals and physicians have increased the number of diagnostic tests, surgical interventions, use of medications, and number of hospitalizations with the sole purpose of making their patients happier. By showing more interest in their patients’ diseases, the hospital and physicians expect to get better scores on the surveys. However, this excess of interventions and expenses does not always ensure the best clinical outcomes. Instead, increased monetary investments can directly affect the finances of the health system.² ³

Currently, 66% of physicians are sheltered under an annual incentive plan; this leads to the idea that “more satisfaction of patients = higher salary.” Many authors consider this to be the silent murderer of the healthcare system since it does not guarantee increased patient satisfaction but it surely guarantees high monetary investment strategies.³

There are two key questions to address as a result of the problems generated by the survey results: How reliable are these surveys? Must we, as healthcare providers, modify our daily clinical practice based on these results? To start, I should mention that from my perspective as a physician, I do not agree that wage benefits and salaries of medical staff should be defined based on these results. More importantly, it should not determine the amount of money provided by the government to the health system and as aid to hospitals.⁵

Up to today, many scientific studies have been conducted to determine the impact of these assessments on the quality of the service in terms of clinical outcomes and patient satisfaction. The findings are controversial because some studies support the hypothesis that there is direct relationship between the scores of the surveys and the quality of healthcare services provided to patients. However, other studies have shown opposite results. There are some key points to be considered to reach a more objective conclusion regarding the implementation of these evaluation systems for medical staff and hospitals.² ⁴

There are many factors involved in each patient’s experience that can affect the general opinion on the quality of his or her medical treatment and how satisfied he or she was with the treatment. Many observers argue that the number of treatments directly correlates with a better perception of the quality of patient care, regardless of the final outcome of the disease. On the other hand, some authors argue that there is a direct relationship between the expected and actual results achieved, thus fulfilling levels of patient expectations.

Based on this relationship, patients judge the effectiveness of physicians and medical staff according to their levels of satisfaction. However, it should be noted that patients receiving a greater number of interventions and treatments do not always get maximum level of satisfaction in spite of all the effort from
the physicians and their teams. In fact, better results have been found on surveys when patients are encouraged to take the leadership of their medical treatment. This leads to better clinical outcomes and a reduction of resources used.

Other factors that may influence the assessment outcomes are: the number of events evaluated per patient (since many of them are chronic patients and have different experiences to be evaluated), the number of physicians involved in the patient care (i.e. different specialties working together), the time between medical care, and the evaluation of that care.3

Despite the variety of studies available in this particular area of knowledge, there is no clear definition of patient satisfaction in healthcare. In turn, many authors are concerned with the patients’ lack of medical knowledge. Therefore, if they receive negative patient comments, they cannot adequately judge and modify their medical practice.

In conclusion, the government must design healthcare reform strategies with all parties in mind. The ultimate goal of these strategies should be to safeguard the healthcare and welfare of patients, not to implement controversial evaluation systems that create conflicts within the system and ultimately lead to detrimental changes in physicians’ clinical practices.

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None

Competing Interests
None declared

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REFERENCES
Anaemia and Haemoglobin A1c level: Is there a case for redefining reference ranges and therapeutic goals?

Segun Adeoye, Sherly Abraham, Irina Erlikh, Sylvester Sarfraz, Tomas Borda and Lap Yeung.

Abstract

Background: Haemoglobin A1c (HbA1c) has been adopted by physicians as a surrogate for monitoring glycemic control. There exists concern that other factors beyond serum glucose concentration may affect glycation rates and by extrapolation HbA1c levels.

Study Objectives: The study attempts to discern clinical differences in HbA1c levels in patients with anaemia compared to patients without anaemia, quantifying and showing the direction of such differences.

Study Design: Using a convenient sampling method and a set of inclusion and exclusion criteria, it examined (retrospectively) patterns in [Hb] and HbA1c in non-diabetics with and without anaemia.

Results: The study observed a statistically significant 0.4 units (8%) difference in the mean HbA1c in anaemia vs. non-anaemic populations. Reference ranges of HbA1c for non-anaemic population and anaemia subtypes was computed. Computed ranges for anaemia group and its subgroups were significantly wider compared to non-anaemia population. Modest but statistically significant correction of anaemia did not result in significant changes in HbA1c.

Discussion: i. The linear relationship between [Hb] and HbA1c holds true for anaemic and non-anaemia populations. ii. Non-diabetic, anaemic have a significantly lower mean HbA1c (5.3% vs. 5.7%), but a similar upper limit of reference range due to a higher variance. iii. The variance and proposed reference ranges for anaemia group and its subtypes was greater than in non-anaemia group, perhaps due to homogenization of clinically heterogeneous entities. iv. Modest correction anaemia did not cause significant change in HbA1c, perhaps the increase in [Hb] was too modest or persistence of correction was too short to be impactful.

Conclusion: It makes the case for defining HbA1c reference ranges for each anaemia subtype, as well as utilizing other surrogates for monitoring glycemic control in populations with anaemia.

Keywords: Anaemia, Haemoglobin A1c, glycosylated Haemoglobin, HbA1c reference range(s), HbA1c therapeutic goals.

Abbreviations: Hb Haemoglobin, HbA1c: glycosylated Haemoglobin, delta sin change

Introduction

The American Diabetic Association (ADA) and the American College of Endocrinology (ACE) recommend HbA1c levels as diagnostic criteria for diabetes mellitus. Physicians have adopted HbA1c levels as a convenient way to screen for diabetes, as well as to monitor therapy. There exists concern that because HbA1c is formed from the glycation of the terminal Valine unit of the β-chain of haemoglobin, it may not be an accurate surrogate to ascertain glycemic control in certain conditions that affect the concentration, structure and function of haemoglobin. It makes logical sense to infer that HbA1c levels should at least in part reflect the average haemoglobin concentration ([Hb]). Kim et al (2010) stated that iron deficiency is associated with shifts in HbA1c distribution from <5.0 to ≥5.5% and significant increases was observed in the patients’ absolute HbA1c levels 2 months after treatment of anaemia. There is a dearth of literature on Hba1c levels in the anaemia population, and a reference range for this unique population does not currently exist. There are a few documented studies on this matter, the findings of which are at best, inconsistent.

It is thought that the various types of haemoglobin found in the myriad of haemoglobinopathies may affect haemoglobin-glucose bonding and/or the lifespan of haemoglobin, and by extrapolation, HbA1c level. Hence, extending target HbA1c values to certain haemoglobinopathies may be erroneous due to potential differences in glycation rates, analytical methods (HbF interferes with the immunoassay method) and some physiological challenges (markedly decreased red cell survival). There is a significant positive correlation between haemoglobin concentration and HbA1c in the patients with haemolytic anaemia. Cohen et al (2008) reported that observed variation in red blood cell survival was large enough to cause clinically important differences in HbA1c for a given mean blood glucose, and haemolytic disorders may cause falsely reassuring HbA1c values. Jandric et al (2012) inferred that in diabetic population with haemolytic anaemia, HbA1c is a very poor marker of both overall glycemia and haemolysis. Mongia et al (2008) report that immunoassay methods for measuring HbA1c may exhibit clinically significant differences owing to the presence of HbC and HbS traits. However, Bleyer et al report that sickle cell trait does not affect the relationship between HbA1c and serum glucose concentration and it does not appear to account for ethnic difference in this relationship in African Americans and Caucasians.
Koga & Kasayama (2010) advise that caution should be entertained when diagnosing pre-diabetes and diabetes in people with low or high haemoglobin concentration when the HbA1c level is near 5.7% or 6.5% respectively, citing the implication of changes in erythrocyte turnover. They further assert that the trend for HbA1c to increase with iron deficiency does not appear to necessitate screening for iron deficiency to ascertain the reliability of HbA1c in this population.11

In the light of the uncertainty in the influence of anaemia and haemoglobinopathies on HbA1c, it is imperative that clinicians are aware of the caveats with HbA1c values when they make management decisions in the anaemic population.12 There is currently a call for the use of other surrogates for ascertaining average glycemic control in pregnancy, elderly, non-Hispanic blacks, alcoholism, in diseases associated with postprandial hyperglycemia, genetic states associated with hyperglycation, iron deficiency anaemia, haemolytic anaemias, variant haemoglobin states, chronic liver disease, and end-stage renal disease (ESRD).13,14

Study objectives and hypothesis

The study attempts to discern clinical differences in HbA1c levels in patients with anaemia compared to non-anaemic population, as well as to quantify and show the direction of such difference if they indeed exist. We hypothesize that as glucose is covalently bound to haemoglobin in glycosylated haemoglobin, HbA1c levels in non-diabetic anaemic population is significantly lower than in non-diabetic, non-anaemic population.2 However, this relationship may not hold true for certain anaemias, haemoglobinopathies and hyperglycation states in some genetic syndromes.

Study design and method

The study is a retrospective chart review of patients with and without anaemia who underwent haemoglobin concentration and HbA1c level testing at The Brooklyn Hospital Center (TBHC) from July, 2009 to June, 2013. Using Cohen (1987) power table, assuming a power of 0.8, alpha level of 0.05, and a small effect size of 0.2 standard deviations (SD), sample size estimation of 461 was computed. A convenient sampling method was used to select patients who meet inclusion criteria, absent exclusionary conditions. In using this sampling method, we queried the electronic medical record at the TBHC using the below-listed inclusion and exclusion criteria. The query generated a list of “potential subjects”. We then reviewed the electronic chart of each patient on this list to confirm that they indeed meet all study criteria (excluding further if any exclusion criteria was identified on “second look”. We continued the selection until the computed minimum sample size of 461 was significantly exceeded. During this process, we had to examine every patient on the “potential subject” list generated by the initial query to achieve this goal. For the purpose of the study, anaemia is defined as haemoglobin concentration <11g/dl.

Inclusion criteria:

• Study participant must be at least 21 years of age. We adopted this age criteria because at TBHC, electronic medical records was only available for the non-pediatric population over the study period. Patients below 21 years were managed at the pediatrics department using paper charts until the recent adoption of the EMR system. It would have been difficult conducting the study using paper charts.
• Study participant must have at least one documented HbA1c level obtained within a month of a haemoglobin concentration assay. This criterion was adopted to allow for more inclusiveness in the study. It is our experience that haemoglobin assays may not be available on the same day as HbA1C assays considering the retrospective nature of the study.

Exclusion criteria:

• Confirmed cases of diabetes mellitus (using two or more of the following: presence of symptoms related to diabetes, fasting blood glucose, 2 hours post-prandial glucose, and oral glucose tolerance test).
• Documented history of gestational diabetes (GDM)
• Documented history of endocrinopathy with affect for glycemic control
• Current or prior use of medication with potential to increase or decrease HbA1c (includes, but not limited to antidiabetics, corticosteroids, statins, and antipsychotics)
• Pregnancy or pregnancy-related condition within three months of HbA1c assay
• Haemoglobin concentration <6 g/dl or >16g/dl.
• Blood loss or blood transfusion within two months of HbA1c assay

The study assumed a consistent HbA1c assay method at the study center over the study period. 482 (229 anaemic and 253 non-anaemic) were selected. The study reviewed electronic medical records of selected patients, extracting data on HbA1c, fasting blood glucose (FBG), 2-hour post-prandial serum glucose (2HPPG), 2-hour post-prandial serum glucose, 2 hours post-prandial glucose, 2 hours post-prandial oral glucose tolerance test (OGTT), haemoglobin concentration and electrophoresis, and anaemia work-up results when available. Subsequent measures of HbA1c two months after correction of anaemia was also documented and compared to pre-treatment levels.

Results and Analysis

The mean age of the anaemic and non-anaemic was 51.8 and 64.6 years respectively. Using the student’s t-test and x² analysis respectively, the difference in mean age of both groups (anaemia and non-anaemia) was significant at p<0.05 while gender distribution was similar (p>0.05), see table 1. The mean HbA1c for anaemic and non-anaemic groups was 5.35% and 5.74% respectively.
respectively, amounting to a 0.4 unit difference in (8%) in mean HbA1c. This difference was statistically significant (p=0.02). A significantly higher variance was observed in the anaemia group (0.79 vs. 0.64).

Table 2: Gender and age distribution and statistics

<table>
<thead>
<tr>
<th>Age in years</th>
<th>(%)</th>
<th>Gender (M/F)</th>
<th>Mean Age (in yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia 21-44</td>
<td>20(8.7)</td>
<td>17/41</td>
<td></td>
</tr>
<tr>
<td>45-64</td>
<td>76(33.2)</td>
<td>43/86</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>133(58.1)</td>
<td>10/32</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>229(100.0)</td>
<td>70/159</td>
<td>54.6</td>
</tr>
<tr>
<td>Non-anaemic 21-44</td>
<td>64(25.3)</td>
<td>23/42</td>
<td></td>
</tr>
<tr>
<td>45-64</td>
<td>134(53.0)</td>
<td>58/81</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>55(21.7)</td>
<td>18/31</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>253(100)</td>
<td>99/154</td>
<td>51.8</td>
</tr>
</tbody>
</table>

p-Values: Age=0.023, Gender=0.061

Assuming that 95% of the population is normal, computation of HbA1c reference range (mean ±1.96SD) for the anaemia and non-anaemia group yielded 3.8-6.9 and 4.5-7.0 respectively. There was a significantly positive spearman correlation between [Hb] and HbA1c (r=0.28, p=0.00). The mean HbA1c level and proposed reference ranges for the five anaemia subgroups (anaemia of chronic disease [ACD], iron deficiency anaemia [IDA], mixed anaemia, macrocytic anaemia and sickle-cell disease) are shown in table 2. Using one-way ANOVA analysis, the difference in the mean [Hb] and HbA1c across anaemia subtypes was not statistically significant (p=0.08 and p=0.36 respectively), see table 2.

Table 2: Anaemia subtypes with HbA1c statistics

<table>
<thead>
<tr>
<th>Anaemia Type</th>
<th>#</th>
<th>Mean [Hb]</th>
<th>Mean HbA1c</th>
<th>95% CI (HbA1c)</th>
<th>Ref. range (HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>92</td>
<td>9.23</td>
<td>5.41</td>
<td>5.24-5.59</td>
<td>3.5-7.1</td>
</tr>
<tr>
<td>IDA</td>
<td>78</td>
<td>9.41</td>
<td>5.38</td>
<td>5.22-5.54</td>
<td>3.9-6.8</td>
</tr>
<tr>
<td>Mixed</td>
<td>11</td>
<td>9.11</td>
<td>5.21</td>
<td>4.82-5.59</td>
<td>3.9-6.5</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>43</td>
<td>8.83</td>
<td>5.14</td>
<td>4.92-5.37</td>
<td>3.7-6.6</td>
</tr>
<tr>
<td>SCD</td>
<td>5</td>
<td>9.12</td>
<td>5.55</td>
<td>4.84-6.26</td>
<td>3.8-7.3</td>
</tr>
<tr>
<td>Anaemia (all types)</td>
<td>229</td>
<td>9.21</td>
<td>5.35</td>
<td>5.24-5.44</td>
<td>3.8-6.9</td>
</tr>
<tr>
<td>Non-anaemic</td>
<td>253</td>
<td>12.87</td>
<td>5.735</td>
<td>5.66-5.81</td>
<td>4.5-7.0</td>
</tr>
</tbody>
</table>

p-values: [Hb] for anaemia subtypes=0.08, HbA1C for anaemia subtypes=0.36, HbA1C anaemia vs. non-anaemia=0.02. ACD: anaemia of chronic disease, IDA: iron deficiency anaemia, SCD: sickle cell disease.

The study also examined the anaemia group to document the effect of anaemia correction on HbA1c levels. Only 62 of the 229 anaemic participants had documented [Hb] and HbA1c after interventions to correct anaemia, see table 3 and 4.

Table 3: Trend in [Hb] and HbA1c

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>Change</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Hb]1</td>
<td>62</td>
<td>9.2</td>
<td>1.07</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Hb]2</td>
<td>62</td>
<td>10.1</td>
<td>1.98</td>
<td>0.25</td>
<td>[Hb]=0.9</td>
<td>0.00</td>
</tr>
<tr>
<td>HbA1c</td>
<td>62</td>
<td>5.37</td>
<td>0.69</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c2</td>
<td>62</td>
<td>5.35</td>
<td>0.66</td>
<td>0.83</td>
<td>HbA1c=0.02</td>
<td>0.78</td>
</tr>
</tbody>
</table>

[Hb]1 and [Hb]2: haemoglobin concentration pre- and post-treatment for anaemia. HbA1c1 and HbA1c2: HbA1c pre- and post-treatment for anaemia

Using the student’s t-test, analysis, a 0.9g/dl mean improvement in [Hb] in the anaemia group (significant at p=0.00) did not result in a statistically significant change in HbA1c (-0.02 units, p=0.78). Similar results were obtained with anaemia of chronic disease and iron deficiency anaemia (ICD: change [Hb]=+0.69g/dl, change HbA1c=-0.09, p=0.31; IDA: change [Hb]=+1.3g/dl, change HbA1c=-0.03, p=0.79).

Discussion

There was an over-representation of the elderly in the anaemia group (58.1% vs. 21.7%). This is not unexpected as nutritional anaemia and anaemia of chronic disease increase in prevalence with the increasing co-morbidities associated with increasing age. The linear relationship between [Hb] and HbA1c holds true for anaemic and non-anaemia populations. There is a statistically significant difference of 0.4units (8%) in the mean HbA1c between the anaemic and the non-anaemic population. This difference is even more marked when the lower limit of the range is compared (3.8 vs. 4.5, difference of 0.7unit, 18%), the significance of which is not as clinically impacting as the upper limit of the range (diabetes mellitus diagnostic criteria). However, the relatively lower limit of normal for HbA1c in anaemic subgroups (especially of anaemia of chronic disease) may make low values of HbA1c in these patients less indicative of over-enthusiastic glycemic control, as well as less predictive of the increase in mortality associated with such tight control.

The upper range of normal for HbA1c for the anaemia and the non-anaemic groups and by extrapolation the proposed diagnostic criteria for diabetes, is however more similar (6.9 vs. 7.0%). This result appear consistent with Koga and Kasavama (2010) assertion that the trend in HbA1c does not appear to change [Hb]=+1.3g/dl, change HbA1c=<0.09, p=0.31; IDA: change [Hb]=+1.3g/dl, change HbA1c=<0.03, p=0.79).

The significantly higher variance (23%) in the anaemia is explained by the heterogeneity of the subtypes within the anaemia group. Perhaps a prospective study that avoids this may report differently.

The significantly higher variance (23%) in the anaemia is explained by the heterogeneity of the subtypes within the anaemia group. The myriad of pathophysiology (from variant...
The study emphasizes the need to exercise caution when applying HbA1c reference ranges to anaemic populations. It makes the case for defining HbA1c reference ranges and thus, applying HbA1c reference ranges to anaemic populations. It highlights the importance of considering the nature of the study, and in our attempt to increase inclusiveness, we allowed haemoglobin concentration and HbA1c assays done within a month of each other. In reality, though, the majority (57%) had the same day assays and even a greater majority (79%) had within the same week assays. We recommend a larger scale prospective study with participants representative of all anaemia subtypes and ages so that the results can be extrapolated to the general population of anaemia patients.

Conclusion

The study examines a large volume of data, eliminating as much as possible, potential extraneous factors in the relationship between [Hb] and HbA1c levels. However, the retrospective nature of the study made the control of other extraneous variables and certain patient attributes infeasible. It was also difficult to discern critical timelines and hence eliminate the potential impact of certain therapeutic interventions. Also, our exclusion of the younger population of patients (i.e. 16-20 years) does not necessarily indicate the results of the study may not be extended to this population of anaemia patients. In fact, the similar human haemoglobin physiology in this group advises that the results may be extended to this younger population without concern. Due to the retrospective nature of the study, we could not ascertain the timelines of certain interventions and hence accurately determine the persistence of anaemia correction. Theoretically, a recent correction in [Hb] is less likely to impact on HbA1c. However, the retrospective nature of the study made the control of other extraneous variables and certain patient attributes infeasible.

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observed in this study). Also, the realized reduced lower limits of reference range in this population will lead to appropriate clinical tolerance for lower HbA1c levels, with avoidance of inappropriate intervention for erroneous perception of over-enthusiastic control of diabetic hyperglycaemia. We recommend that, absent risks factors for and symptoms relatable to diabetes, marginal elevations in HbA1c levels (i.e. HbA1c >6%) in anaemic patients should warrant confirmation of diagnosis using fasting blood glucose and 2HPPG or OGTT. The use of other surrogates of glycemic control, immune to the blur associated with haemoglobin type and concentration, may circumvent the problem associated with use of HbA1c in this special population. To this end, fructosamine and glycated albumin assays are currently being examined. 1,15

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Competing Interests
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REFERENCES


Frequency and severity of depression among mothers of children with cancer: Results from a teaching hospital in Karachi, Pakistan

Mariam Ghufran, Marie Andrades and Kashmira Nanji

Abstract

Background: Diagnosis of cancer in one’s child causes not only social but also psychological devastation for the whole family especially mothers. Depressed mothers are less able to help their sick child cope with intensive treatments. This study was done to identify frequency and severity levels of depression in mothers of children with cancer.

Methods: A cross sectional study was conducted from September 2011-March 2012 at Aga Khan University Hospital, pediatric oncology clinics. Hundred mothers were enrolled according to inclusion and exclusion criteria. A pre-coded validated questionnaire regarding mothers and child’s demographics along with Hamilton-D (HAM-D), a depression screening and severity scale, was used. Data was analyzed using SPSS (19.0), frequencies, and proportions were reported accordingly.

Results: Forty-three percent mothers were in the age group of 30-39 years. Seventy-eight percent mothers were found to be depressed. Out of those 69% had mild, 25% moderate, 5% severe, and 1% had very severe depression.

Conclusion: Majority of mothers were found to be depressed in this study. This known high level of depression in mothers, it is recommended that early non-therapeutic and/or therapeutic interventions should be done to help them cope with their situation.

Keywords: Mothers, Cancer Children, Caregiver Depression

Abbreviations: AKUH (Aga Khan University Hospital), HAM-D (Hamilton-Depression Scale), WHO (World Health Organization), CDC (Centers for Disease Control and Prevention), ALL (Acute Lymphoblastic Leukemia), SPSS (Statistical Package For Social Sciences), US (United States), GNP (Gross National Product), NCI (National Cancer Institute), SD (Standard Deviation), SEER (Surveillance Epidemiology and End Results), CI (Confidence Interval), OR (Odds Ratio)

Introduction

Currently, depression is the leading cause of disability in the world and is predicted to become the second largest killer after heart disease by the year 2020. Eighty percent of individuals with depression report functional impairment while 27% report serious difficulties at work and home life. According to a study conducted in 2011, India has the highest rate of depression (36%) in low income countries with women being affected twice more than men. Cancer in children occurs randomly and spares no ethnic group, socio-economic class, or geographical region. An estimated 11,630 new cases are expected to occur among children aged 0-14 years in 2012 in the US, out of which 1,310 will die by end of 2013 due to it. Based on Karachi Cancer Registry it is estimated that about 7500 children get cancer every year in Pakistan. The mortality rates for childhood cancers have declined by 68% over the past four decades, from 6.5 per 100,000 in 1969 to 2.1 in 2009. However, the diagnosis of cancer in one’s child marks the beginning of social and psychological devastation for the whole family especially the mother. The length and intensity of treatment can be as distressing as the disease itself, negatively affecting their functionality as parents and in turn the child’s ability to handle the treatment. As a primary care provider mother’s responsibility increases substantially starting a vicious cycle of anxiety and socio-economic uncertainty leading her to depression much more than the father. The available data supports that mothers of children with cancer represent a group prone to high levels of emotional distress, and that the period following their child’s diagnosis and the initiation of treatment may be predominantly stressful and disturbing leading them to depression. Such mothers have difficulty in taking care of themselves, their household and especially their sick children. Many parents continue to suffer from clinical levels of distress, even after five years off treatment of their child. Many studies have shown that chronic depression and distress may lead to decrease in immune functioning and an increased risk of infectious disease in healthy individuals. Mothers are generally with the child mainly and hence are most affected from their child’s disease. In this study, we intended to estimate the frequency and severity of depression in mothers having children with cancer.

There is limited evidence from Pakistan regarding depression in mothers of children with cancer. The previous studies conducted had certain limitations such as small sample size, assessment of depression in both parents and that too of children with leukaemia only. This study intends to determine the frequency and severity of depression among mothers of children with cancer.

Methods

A cross sectional survey was conducted in the paediatric oncology clinics at The Aga Khan University Hospital, a
teaching hospital in Karachi over a period of six months (September 2011- March 2012). Mothers of children with cancer were enrolled in the study, consecutively according to the inclusion and exclusion criteria. Mothers having children less than 15 years of age with any type of cancer, diagnosed by oncologist (2 months after diagnosis to rule out bias for normal grief period)12, mothers bringing their sick child for the first time to the teaching hospital or as follow up or for day care oncology procedures were included in the study. Mothers who had existing psychiatric illness (and or already diagnosed as having depression by a doctor) and/or taking medications for it, any recent deaths in family (within six months of interview) or having other co-morbidities (malignancy, myocardial infarction in previous year, neuromuscular disease limiting ambulation or blindness) were excluded.

A pre-coded validated and structured Urdu13, 14 and English15, 16 version of the questionnaire was used for data collection the questionnaire took about 20 minutes to complete and consisted of two sections. Section A included mother’s and child’s demographic details and treatment status. Section B, consisted of Hamilton Depression Rating Scale (HAM-D 17) a validated scale (sensitivity 78.1% and specificity 74.6%) for assessing frequency and severity of depression in both hospitalised patients and the general population15. Scores of \( \geq 7 \) indicate no depression and scores \( > 7 \) are labelled as depressed. Mothers who were found to be depressed were further classified into mild (scores 8-13), moderate (scores 14-18), severe (scores 19-22) and very severe depression (scores \( \geq 23 \))16. Mothers with mild to moderate depression were referred to the family physicians; those with severe, very severe, or suicidal tendencies were urgently referred to a psychiatrist.

Institutional Ethical Committee of the Aga Khan University Hospital approved the study. Confidentiality of participants was maintained and informed written consent was obtained.

Sample size calculated by WHO software. The prevalence of maternal depression ranges from 56.5% to 61.5%17, 18 as evident from different international studies. With 95%, confidence interval and bound on error of 10% the sample size came out to be 95. After an addition of 5% for non-responders, the total required sample size was 100 study participants. Data was double entered and analyzed in SPSS version19. The outcome variable was dichotomized as no depression and depression (cut off score7). Analysis was performed by calculating frequencies of categorical variables (maternal age, education, current marital status, employment, co-morbidities, diagnosed depression and treatment in mother, number of children, gender of sick child, cancer type, time since diagnosis of cancer in child, treatment given so far and current treatment status of child and family income). Means and Standard Deviation was reported for current age of the child.

Results

One hundred and sixty mothers were approached out of which 100 mothers consented to participate in the study yielding a response rate of 62.5% (100/160). With regards to the mothers the most common age group was the 30-39 year old category (43%). Fifty-five percent of mothers had a high level of education (those who had completed class 11-12 or engaged in professional education). Nearly all the mothers (98%) were married and were homemakers (95%). Only 5% of mothers were working outside the home. More than half of the participants (57%) had one to three children while 43% had more than three. Monthly financial income for 65% of the participants were more than fifty thousand Pakistani rupees (Table 1).

Table 1: Demographic Characteristics of Mothers (N=100)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of mother</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29 years</td>
<td>39</td>
<td>39.00%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>43</td>
<td>43.00%</td>
</tr>
<tr>
<td>40 years and above</td>
<td>18</td>
<td>18.00%</td>
</tr>
<tr>
<td><strong>Education Level of mothers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>13</td>
<td>13.00%</td>
</tr>
<tr>
<td>Primary/secondary/intermediate</td>
<td>32</td>
<td>32.00%</td>
</tr>
<tr>
<td>Higher</td>
<td>55</td>
<td>55.00%</td>
</tr>
<tr>
<td><strong>Marital status of mothers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently Married</td>
<td>98</td>
<td>98.00%</td>
</tr>
<tr>
<td>Divorced</td>
<td>1</td>
<td>1.00%</td>
</tr>
<tr>
<td>Widow</td>
<td>1</td>
<td>1.00%</td>
</tr>
<tr>
<td><strong>Maternal Employment Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>95</td>
<td>95.00%</td>
</tr>
<tr>
<td>Working</td>
<td>5</td>
<td>5.00%</td>
</tr>
<tr>
<td><strong>Number of children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>57</td>
<td>57.00%</td>
</tr>
<tr>
<td>More than 3</td>
<td>43</td>
<td>43.00%</td>
</tr>
<tr>
<td><strong>Family Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20,000</td>
<td>4</td>
<td>4.00%</td>
</tr>
<tr>
<td>20,000-50,000</td>
<td>31</td>
<td>31.00%</td>
</tr>
<tr>
<td>&gt; 50,000</td>
<td>65</td>
<td>65.00%</td>
</tr>
</tbody>
</table>

* (Not Educated: Those who do not have primary education, Primary 1-5 years of schooling, Secondary: 6 to 10 years of schooling, Intermediate: Who have studied class 11 and 12, Higher: Who have completed or engaged in professional education)

The demographic characteristics of child are detailed in Table2. Seventy-five percent of sick children were male while 25% were females (n=100). Half the children were diagnosed with cancer between the age of three to nine. Fifty percent of children (n=50), had their diagnosis of cancer in the last one to five years. More than half of children (57%) were on treatment during study phase. Different types of cancers occurring in children are shown in Figure 1.

Seventy eight percent of the mothers were depressed. Sixty-nine percent (n= 54) had mild depression, nearly 25% (n=19) had moderate, while 5% (n= 4) had severe and 1% (n=1) had very severe depression. (Table 3)
The prevalence of depression in mothers in this study was as high as 78%. Mild depression was seen in 69% of mothers, moderate in 25%, severe in 5% while 1% had very severe depression. This high prevalence of depression in such mothers has not been reported from Pakistan before. The soaring levels of depression however have been consistent with the study conducted in Turkey in 2009 in mothers of children with leukaemia where 88% (n=65) were depressed. Mild depression was reported in 22.7% (n=18) and major depression in 61.5% (n=40). Similar results were reported from a study conducted on both parents of children with leukaemia in 2002 in Pakistan where 65% (n=60) of mothers were found to be depressed. Nevertheless, severity of depression in this study was not noted. A Sri Lankan study in 2008, showed moderate to severe depression to be 22.9% and 21.9% in mothers having children with mental and physical disorders respectively. Another study conducted in Florida in 2008 suggests that an increased symptom of depression in mothers is related to significantly lower ratings in quality of life for their children.

The existing data supports the argument that mothers of children with cancer represent a group prone to high levels of emotional distress. The time following their child’s diagnosis and the commencement of treatment may be particularly stressful and traumatic with an incidence as high as 40%.

There could be multi-factorial reasons for this alarmingly high rate of depression seen in Pakistani mothers. One of the causes could be the political instability that Pakistan has been facing for past few years leading to economic volatility. The study conducted in 2002 in Karachi saw 65% of maternal depression which has now risen to 78% in this study. Due to political unrest, everyday strikes, bombasts, these mothers may also have difficulty in reaching hospital on scheduled visits leading to postponement of treatment. Other reason could be economic inflation. The cost of daily living has soared while allocated medical budget was 0.27% of its gross domestic product (GDP) on health in 2011-12, which is insufficient to cater the needs of the population (Economic Survey of Pakistan of 2011-2012).

Lately, there has been a recent trend towards nuclear families in Pakistan rather than living in extended families as before. This in turn may lead to mother being the soul person in looking after the sick and her healthy children as well as managing house chores and doctor’s appointments leading to more frustration. This study also showed that 57% mothers had three children while 43% had more than three children. This could also be one of the factors for high rate of depression as looking after multiple children is demanding and may lead to decreased coping skills of mothers.

Other possible reason for this high rate of depression could be that mostly educated mothers were visiting the hospital that have access to internet and can search up all details, good or bad, on their child’s disease. This may start a vicious circle of worry for mothers. Other possible reasons for this growing depression could be gender of child (as in this society male child is thought to be the support and bread earner of the family),

### Table 2: Demographics and social characteristics of sick child (N=100)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age of child *</td>
<td></td>
<td>6.90 (±3.40)*</td>
</tr>
<tr>
<td>Gender of Sick Child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75</td>
<td>75.0%</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>25.00%</td>
</tr>
<tr>
<td>Age of child at cancer diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 months-3 years</td>
<td>40</td>
<td>40.0%</td>
</tr>
<tr>
<td>3-9 years</td>
<td>50</td>
<td>50.00%</td>
</tr>
<tr>
<td>More than 9 years</td>
<td>10</td>
<td>10.00%</td>
</tr>
<tr>
<td>Time since diagnosis of child’s cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>15</td>
<td>15.0%</td>
</tr>
<tr>
<td>1-5 years</td>
<td>50</td>
<td>50.00%</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>35</td>
<td>35.00%</td>
</tr>
<tr>
<td>Current treatment status of child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment</td>
<td>57</td>
<td>57.0%</td>
</tr>
<tr>
<td>Off treatment</td>
<td>43</td>
<td>43.00%</td>
</tr>
</tbody>
</table>

*Others (BLL, Rhabdomyosarcoma, Glioblastoma, Nephroblastoma)

### Table 3: Frequency and levels of severity of Depression in mothers

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of Depression (n=100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression present</td>
<td>78</td>
<td>78%</td>
</tr>
<tr>
<td>Depression absent</td>
<td>22</td>
<td>22%</td>
</tr>
<tr>
<td>Severity of Depression (n=78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>54</td>
<td>69%</td>
</tr>
<tr>
<td>Moderate</td>
<td>19</td>
<td>25%</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>Very severe</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

### Discussion

Depressed patients are frequently encountered in nearly all specialty clinics. However, depression in caregivers accompanying patients is usually overlooked and hence missed, as doctors are mostly focused on the patient’s evaluation, condition, and treatment. When the patient is a child and the diagnosis is cancer, this difficult circumstance has a sudden and long term impact on both the child and the family. Many parents of a child with cancer will have very strong feelings of guilt. As such, parents of cancer survivors may be at risk for impaired physical and mental health. An increasing body of literature supports the conclusion that various levels of parental distress are ongoing, long after treatment is completed.

The prevalence of depression in mothers in this study was as high as 78%. Mild depression was seen in 69% of mothers,
child’s current treatment status and time since diagnosis of cancer in child.

Strengths and Limitations

To the best of authors’ knowledge, this study has touched upon a topic that was not yet been attended to, in local context. Moreover, in this study adjustment phase of two months, for acute stress and posttraumatic stress disorder was given for diagnosis of depression in mothers. It was done to rule out bias in study. HAM-D also focuses on symptoms in the past 1 week, to minimize the recall bias. The findings in this study offer evidence and importance of the need for developing psychological support for families especially mothers who are caring for a child with cancer, in Pakistan.

This study has several limitations. The study was conducted in a tertiary care private hospital, which mostly caters a specific segment of population. Hence, the results may not be a true representation of the population. All data in this study was self-reported by the participants. Thus, it is anticipated that there may be some bias in their responses and recall. Lastly, since this was a cross-sectional study so temporality is difficult to establish.

Conclusion

In conclusion more than three-fourth of our study participants were depressed.

The outcome is expected to identify depressed mothers so that effective strategies can be developed to enhance their coping skills and medically treat them when required. This in the long term is expected to increase quality of life for both their sick and healthy children as well as mothers themselves.

Future Research and Policy Recommendations

Future studies are recommended in order to confirm our findings. Such studies need to be conducted on a larger scale, at national level, in various hospitals and settings to counteract limitations of our study with appropriate means of measuring depression in mothers. Factors, not explored in this study such as personality styles and coping skills of mothers can be explored as these may be significant aspects leading to depression. Further co-morbidities, such as anxiety and posttraumatic stress disorder symptoms related to child’s cancer should also be investigated.

Other associated factors, such as the political and economic situation, which perhaps may also be a leading cause of depression in our part of the world, should also be assessed. Simultaneously, measures should be taken to root such factors out at national levels.

The results of current study show the need of incorporating mothers into a treatment process designed for psychological interventions, not only after the diagnosis of cancer in their child but also during their child’s treatment. Psychosocial services should be recognised as an important constituent of comprehensive cancer care for families of children with cancer.

It is highly advocated that the healthcare professionals who work with the families of children with cancer should evaluate the children and their families concerning the psychological and social aspects of their lives. Arrangements for family counselling for those needing help should be made. Mothers should also be referred to family physicians and social support if available. The mother’s crucial position in the family and the proximal and distal effects of her adaptation to the crisis of cancer in the family should lead to the design of interventions intended at decreasing her distress and at promoting her adaptive coping skills as improving mothers’ problem-solving skills has been associated with reductions depression and anxiety\(^\text{28}\). Thus, all hospitals, dealing with paediatric cancer cases should have a family counselling and support system.

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Competing Interests

None declared

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Physical activity after cancer: An evidence review of the international literature

Robert James Thomas, Mea Holm and Ali Al-Adhami

Abstract

The importance of physical activity during and after cancer treatments is now being appreciated, as emerging evidence suggests that it improves several common side-effects of cancer treatments, as well as correlating with improving overall survival and reduced the probability of relapse. The biological mechanisms through which these benefits are achieved may include effects on cell growth regulatory pathways, levels of hormones, gene expression patterns and tumour immunity. Here we review the evidence for the benefits of exercise during and after cancer, discuss the possible underlying biological mechanisms, and suggest ways in which this knowledge may be used to improve mainstream care of cancer patients.

Keywords: Exercise, cancer, survival, side effects

Introduction

The number of individuals surviving cancer is expected to rise by one-third according to estimates from the American Cancer Society and the National Cancer Institute. This means that in the UK over 3 million individuals, and in the USA over 18 million individuals, will be living with the consequences of cancer by 2,022. The increase in the number of survivors is attributed to earlier diagnosis, an aging population, better cure rates and more effective systemic therapies to keep patients with metastatic disease alive for longer. To achieve these benefits, patients often have to endure more complex and arduous therapies, frequently leaving them beleaguered with acute and long-term adverse effects. In addition to being unpleasant, these adverse effects result in financial implications for patients and their families, as well as resulting in a greater usage of health resources.

Although the importance of exercise is beginning to be recognised by health professionals, advocacy groups and charities, it still remains an under-utilised resource. This article highlights the evidence that a physically active lifestyle and formal exercise programmes can help relieve many of the common concerns and adverse effects which plague individuals in the cancer survivorship period.

Physical activity improves well-being after cancer

Dozens of interventional studies have tested the feasibility and potential benefits of exercise in cancer survivors. Recent meta-analyses of randomised trials involving exercise interventions after cancer, encouragingly demonstrate that the benefits of exercise spanned across several common cancer types and following a range of treatments including surgery, radiotherapy, chemotherapy, hormones and even the newer biological therapies. The most recent meta-analysis of 34 randomised trials published in the BMJ in 2012 involving patients exercising after cancer, demonstrated a benefit for a number of troublesome symptoms particularly fatigue, mood, anxiety and depression; muscle power, hand grip, exercise capacity and quality of life.

The American College of Sports Medicine also published a comprehensive review of exercise intervention studies in cancer populations which included data from 85 RCT’s of exercise in cancer survivors. Evidence consistently demonstrated that exercise could be performed safely in adjuvant and post-treatment settings. Exercise led to significant improvements in aerobic fitness; increased flexibility and strength; quality of life; anxiety and depression; fatigue, body image, size and composition.

The individual categories of symptoms which commonly afflict cancer survivors are now discussed in more detail:

Cancer related fatigue (CRF) is one of the most distressing symptoms experienced by patients during and after their anticancer therapies. It is reported by 60-96% of patients during chemotherapy, radiotherapy or after surgery, and by up to 40% of patients taking long-term therapies such as hormonal or biological therapies. The first step to treating CRF is to correct, if possible, any medical conditions that may aggravate it, such as anaemia, electrolyte imbalance, liver failure and nocturia; or to eliminate drugs such as opiates, anti-histamines and anti-sickness medication. The role of exercise was reviewed in 28 randomised, controlled trials (RCTs) involving 2083 patients exercising after cancer, demonstrating a benefit for a number of troublesome symptoms particularly fatigue, mood, anxiety and depression; muscle power, hand grip, exercise capacity and quality of life.
participants in a variety of exercise programmes and showed that exercise improved CRF, although the benefit overall was small. A second review of 18 RCTs involving 1,109 participants, sub-divided the data into types of exercise and demonstrated that supervised exercise programmes had the most impact on CRF. Further meta-analyses and reviews have also showed that supervised exercise programmes had better results, with a greater reduction in CRF amongst breast cancer survivors assigned to exercise programmes compared to home-based programmes.

Psychological distress, including anxiety and depression, is common after cancer with reported prevalence rates of 25-30%. Patients with psychological distress have also been shown to have reduced survival compared to those who are psychologically healthy. Exercise may help alleviate this symptom and improve mood, as a number of observational studies have shown that cancer patients who exercise have reduced levels of depression and anxiety, better self-esteem and are happier, especially if they involve group activities. The recent meta-analyses of RCTs also demonstrated a reduction in anxiety and depression among individuals assigned to exercise programmes.

Quality of life (QOL) is lower in many cancer sufferers and survivors, linked to other physical and psychological symptoms of cancer and its’ treatment. Meta-analyses of studies of exercise intervention programmes have demonstrated an improvement of QOL at all stages of the illness for the common cancer types and following several types of treatment. For example, in a study involving 1,966 patients with colorectal cancer, patients achieving at least 150 minutes of physical activity per week had an 18% higher QOL score than those who reported no physical activity, as measured by the QOL FACT-C. Another study showed similar benefits for breast cancer survivors who had completed surgery, radiotherapy or chemotherapy, and also demonstrated that change in peak oxygen consumption correlated with change in overall QOL.

Weight gain: 45% of women with breast cancer report significant weight gain, and in a study of 440 prostate cancer survivors, 53% were overweight or obese. For patients with bowel cancer, the CALBG 8980 trial showed that 35% of patients post-chemotherapy were overweight (BMI 25.0–29.9), and 34% were obese (BMI 30.0–34.9) or very obese (BMI >35). The reasons for this are multifactorial, but may include other symptoms of cancer treatment such as fatigue and nausea, causing patients to stop exercising. Regardless of the reasons for weight gain, numerous reviews and a comprehensive meta-analysis of the published literature have demonstrated that individuals who gain weight after cancer treatments have worse survival and more complications. Fortunately, supervised exercise programmes have been shown to reduce weight and have significant other benefits on body constitution and fitness, such as improved lean mass indices, bone mineral density, cardiopulmonary function, muscle strength and walking distance.

Bone mineral density (BMD): Pre-menopausal women who have had breast cancer treatment are at increased risk of osteoporosis, caused by reduced levels of oestrogen brought on by a premature menopause due to chemotherapy, surgery or hormones. Men who receive hormone deprivation therapy for prostate cancer are also at an increased risk of developing osteoporosis. Accelerated bone loss has also been reported for many other cancers, including testicular, thyroid, gastric and CNS cancers, as well as non-Hodgkin’s lymphoma and various haematological malignant diseases. Lifestyle factors linked to an increase in the risk for developing osteoporosis include a low calcium and vitamin D intake, a diet low in plant-based protein, lack of physical activity, smoking and excessive alcohol intake. A number of studies have linked regular physical activity with a reduction in the risk of bone mineral loss. Sixty-six women with breast cancer were randomized to a control group or an exercise programme. The rate of decline of BMD was -6.23% in the control group, -4.92% in the resistance exercise group, and -0.76% in the aerobic exercise group. The statistically significant benefit was even greater in pre-menopausal women. In another RCT of 223 women with breast cancer, it was found that exercise, over 30 minutes 4-7 times a week, helped preserve bone mineral density even when bisphosphonates (risedronate), calcium and vitamin D had already been prescribed.

Thromboembolism: Those with pelvic involvement, recent surgery and immobility, previous history of varicose veins or thrombosis or receiving chemotherapy, are at higher risk. Although strategies such as compression stockings, warfarin and low molecular weight heparin are essential, early mobilisation and exercise remains a practical additional aid in reducing this life-threatening complication.

Constipation caused by immobility, opiate analgesics or anti-emetics during chemotherapy is a significant patient concern. Exercise reduces bowel transit time, and ameliorates constipation and its’ associated abdominal cramps.

Physical activity improves survival and reduces relapse

In addition to improving the side effects of treatment for cancer, regular physical activity during and after cancer appears to improve overall survival and reduces the probability of relapse. One of the most convincing studies was an RCT in which 2,437 post-menopausal women with early breast cancer...
were randomised to nutritional and exercise counselling, or no counselling, as part of routine follow-up. In the group receiving counselling, fewer women relapsed and overall survival was greater in the oestrogen-negative subgroup. In another RCT, men with early prostate cancer were randomised to an exercise and lifestyle intervention or standard active surveillance. The average PSA in the intervention group went down, whilst in the control group it went up. This supports a previous RCT of which the primary end point evaluated a salicylate-based food supplement, but it required men in both arms to receive exercise and lifestyle counselling. Although there was no difference in the primary end point, 34% of men, who’s prostate specific antigen (PSA) was climbing before trial entry, stabilized.

The majority of the other published evidence for a reduced relapse rate and improved survival after cancer originates from retrospective analysis or prospective cohort studies. The National Cancer Institute, in a recent meta-analysis, reviewed 45 of these observational studies. The strongest evidence was demonstrated for breast cancer survivors; the next strongest evidence was for colorectal cancer survivors, followed by prostate cancer. The most notable are summarised below:

**Breast cancer:** The five most prominent prospective cohort studies (in aggregate more than 15,000 women), have examined the relationship between physical activity cancer and prognosis:

- Irwin et al. (2008) investigated a cohort of 933 breast cancer survivors and found that those who consistently exercised for >2.5 hours per week had a 67% lower risk of all deaths compared to sedentary women.
- Holmes et al. (2005) performed a separate evaluation of 2,987 women in the Nurses’ Health Study and found that women walking >3 hours a week had lower recurrence rates, and better overall survival.
- Holick et al. (2008) performed a prospective observational study of 4,482 breast cancer survivors, and found that women who were physically active for >2.8 hours per week had a 35-49% lower risk of dying from breast cancer.
- Pierce et al. (2007) found that the benefits of 3 hours of exercise were even greater if combined with a healthy diet.
- Sternfeld et al. (2009) in the LACE study, evaluated 1,870 women within 39 months of diagnosis. There was a significant difference in overall death rate between the highest and lowest quartile of exercise levels.

**Colorectal cancer:** The scientific community eagerly awaits the results of the CHALLENGE RCT mentioned above, but a number of retrospective analyses of randomised chemotherapy and cohort trials have been published:

- Haydon et al. (2006) retrospectively analysed a RCT involving patients with stage III bowel cancer and found a significant association between exercise and a 31% reduction in relapse rate.
- Giles et al. (2002) found that of 526 patients recruited into the Australian Cohort Study, those participating in recreational sport 1-2 days per week had a 5 year overall survival of 71%, as opposed to 57% in non exercisers.
- Meyerhardt et al. (2006) found in an analysis of the Intergroup CALGB study, that physically active patients with bowel cancer had 35% reduction in relapse rate in after chemotherapy.
- Meyerhardt et al. (2009) analysed 668 patients with colorectal cancer within the Health Professionals Study. Men who exercised >27 vs. < 3 METS-hours / week had a lower cancer-specific mortality.

**Prostate cancer:** Three cohort studies have demonstrated a survival benefit for physically active men with prostate cancer:

- Kenfield et al. (2011) performed a subset analysis of 2,686 men with prostate cancer, within the Health Professionals Study, who exercised >30minutes per week or >3 MET-hours of total activity, had a 35% lower risk of overall death, and men who walked at a brisk pace for >90 minutes had a 51% lower risk of overall death.
- Richman et al. (2011) reported that 1,455 men with prostate cancer, walking more than 3 hours a week, correlated with an improved survival but only if >3miles/hour.
- Giavannucci (2005), within a prospective analysis, reported that men who exercised vigorously had a lower risk for fatal prostate cancer, although this effect was only seen for men over the age of 65.

**Quantity and type of exercise recommended for cancer patients**

For reduced cancer relapse and improved well-being, most of the cohort studies summarized above suggest moderate exercise of around 2.5 to 3 hours a week for breast cancer survivors. However, for prostate cancer survivors, mortality continues to decrease if the patient walks 4 or more hours per week, and more vigorous activity is also associated with significant further reductions in risk for all-cause mortality. When the mode of exercise is primarily walking, a pace of at least 3 miles/hour (for >3 hours/week) is recommended for a reduced risk of relapse. Therefore, both the pace and duration of exercise affect the survival benefit achievable from exercise, with more vigorous activity generally having a greater benefit (see Table 1). The best results appear to be with programmes including a combination of aerobic and resistance exercises, particularly within a social group.
Table 1: Summary of exercise guidelines for cancer survivors

- Exercising for >3 hours/week has proven benefits for cancer survival
- A pace of at least 3 miles/hour when walking provides greater benefit than a slower pace
- For optimal benefit, exercise should consist of a combination of resistance and aerobic exercises
- Supervised exercise programmes have shown greater benefits for cancer survivors than home-based programmes

Table 2: Summary of the potential biochemical pathways of the anticancer effects of exercise

<table>
<thead>
<tr>
<th>Class of Effector Molecule</th>
<th>Effector Molecule</th>
<th>Effects of Exercise on Effector Molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell growth regulators</td>
<td>IGF1</td>
<td>Decreased levels</td>
</tr>
<tr>
<td></td>
<td>IGFBP3</td>
<td>Increased levels</td>
</tr>
<tr>
<td>Proteins involved in DNA damage repair</td>
<td>BRCA1</td>
<td>Increased expression</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>Increased expression</td>
</tr>
<tr>
<td>Regulator of apoptosis and cell cycle arrest</td>
<td>p53</td>
<td>Enhanced activity</td>
</tr>
<tr>
<td>Hormones</td>
<td>Oestrogen</td>
<td>Decreased levels</td>
</tr>
<tr>
<td></td>
<td>Vasoactive intestinal protein (VIP)</td>
<td>Decreased levels</td>
</tr>
<tr>
<td></td>
<td>Leptin</td>
<td>Decreased levels (indirect)</td>
</tr>
<tr>
<td>Immune system components</td>
<td>NK cells</td>
<td>Enhanced activity</td>
</tr>
<tr>
<td></td>
<td>Monocyte function</td>
<td>Enhanced activity</td>
</tr>
<tr>
<td></td>
<td>Circulating granulocytes</td>
<td>Increased proportion</td>
</tr>
</tbody>
</table>

The precise amount of exercise has to be determined on an individual basis and depends on pre-treatment ability, current disability caused by the cancer itself or the treatment, as well as time proximity to major treatments. An exercise programme supervised by a trained professional has major advantages, as they can design a regimen which starts slowly and gradually builds up to an acceptable and enjoyable pace. In addition, they can help motivate the individual to continue exercising for the short and the long-term, and they can judge the optimal exercise levels to improve fatigue, and not aggravate it.

The underlying mechanisms of the potential anti-cancer effects of exercise

The body’s chemical environment significantly changes after exercise, best demonstrated in the Ornish study, which found that serum from prostate cancer patients who exercised, had an almost eight times greater inhibitory effect on the growth of cultured androgen dependent prostate cancer cells compared to serum from patients in the control group. The precise chemical mechanism, which the anti-cancer effect remains incompletely understood, but one of the most likely mechanisms involving growth factors such as insulin-like growth factor (IGF-1) and its' binding proteins insulin-like growth factor binding proteins (IGFBPs), due to the central role of these proteins in the regulation of cell growth (see Table 2). After binding to its receptor tyrosine kinase, IGF-1 activates several signalling pathways including the AKT pathway, leading to the inhibition of apoptosis and the promotion of cell growth and angiogenesis. An inverse relationship of cancer risk with IGFBP3 levels has also been shown, although this effect has not been confirmed in all studies. Exercise has been shown to increase the levels of IGFBP3, and this was associated with a 48% reduction of cancer-specific deaths in a large prospective cohort study of 41,528 participants. Decreased levels for IGF-1 in physically active patients have been reported with an associated survival benefit.

Exercise has also been shown to have a large impact on gene expression, although the mechanisms through which the patterns of gene expression are affected remain to be determined. In a recent study of the mechanisms through which exercise impacts prostate cancer survival, it was found that 184 genes are differentially expressed between prostate cancer patients who engage in vigorous activity, and those who do not. Amongst the genes that were more highly expressed in men who exercise were BRCA1 and BRCA2, both of which are involved in DNA repair processes.

Another neuropeptide which changes after exercise is Vasoactive Intestinal Protein (VIP). Breast and prostate cancer patients have been found to have higher VIP titres compared to individuals who regularly exercise, and who have increased production of natural anti-VIP antibodies. In hormone-related cancers such as cancers of the breast, ovaries, prostate and testes, the association between high levels of circulating sex hormones and cancer risk is well established. Another mechanism through which exercise may affect cancer, is through decreasing the serum levels of these hormones. For breast cancer survivors, the link between exercise and lower levels of oestrogen has been shown. An indirect, related mechanism is that exercise helps reduce adiposity, and adiposity in turn influences the production and availability of sex
hormones. In addition, greater adiposity leads to higher levels of Leptin, a neuropeptide cytokine with cancer promoting properties.

Other pathways include the modulation of immunity, such as improvements in NK cell cytolytic activity; the modulation of apoptotic pathways through impacting on a key regulator, p53, and an exciting recent discovery, the messenger protein irisin, which is produced in muscle cells in response to exercise and is found to be an important molecule in linking exercise to the health benefits. However, we are only beginning to scratch the surface with these and the other mechanisms discussed here, and much more research needs to be done to in this area.

Incorporating exercise into mainstream cancer management

The challenge for health professionals is how to encourage and motivate individuals with cancer to increase their exercise levels. Some, of course, are motivated to increase physical activity or remain active after cancer. However, a recent survey of 440 men with prostate cancer found that only 4% of patients exercised for more than the 3 hours a week recommended by the WCRF. Macmillan Cancer Relief has produced a series of helpful booklets and web-based patient information materials designed to inform and motivate individuals to exercise as part of its ‘Move More’ programme. The Cancernet website has a facility to search for local exercise facilities by postcode, which can be an aid for health professionals when counselling patients. It highlights activities that men will hopefully find feasible and enjoyable such as golf, exercise groups and walking groups, and are encouraged to attend in addition to work place activity and gardening.

Several pilot schemes have been started throughout the UK with the aim to incorporate exercise programmes into standard oncology practice. The difficulty with small schemes is that they tend to be poorly funded, often poorly attended and are unlikely to be sustainable in the longer term. Many agree that the gold standard model would be similar to the cardiac rehabilitation programme. This would involve a hospital scheme run by a physiotherapist or an occupational therapist, supervising patients immediately after surgery, radiotherapy and during chemotherapy. This is followed by referring the patient to a community-based scheme for the longer term. Unfortunately, this type of scheme is expensive and unlikely to be funded at present, despite the obvious savings by preventing patient relapsing and utilising health care facilities to help late effects of cancer treatment. However, expanding existing services, such as the National Exercise Referral Scheme, is a practical solution. The National Exercise Referral Scheme exists for other chronic conditions such as cardiac rehabilitation,

obesity and lower back pain. The national standards for the scheme to be expanded to include cancer rehabilitation were written and accepted in 2010. Training providers have now developed training courses for exercise professionals set against these standards. Trainers completing the course gain a Register of Exercise Professionals (REP’s) Level Four qualification, allowing them to receive referrals from GPs and other health professionals.

Conclusion

There are a wealth of well-conducted studies which have demonstrated an association between regular exercise and lower risk of side effects after cancer, as well as reasonable prospective data for a lower relapse rates and better overall survival. However, as there are several overlapping lifestyle factors, which are difficult to investigate on their own, there remain some concerns that exercisers may do better in these studies because they are less likely to be over-weight, more likely to have better diets and to be non-smokers. Although the existing RCTs provide encouraging evidence that exercise intervention programmes are beneficial, further large RCTs are needed, particularly in terms of cost-effectiveness, before commissioner’s start investing more in this area.

Competing Interests
None declared

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An unusual reaction to IV pethidine - A Case Report

Prakash Krishnan and Asquad Sultan

Abstract
Pethidine is used in some centres for post operative rescue analgesia, among other indications. We report an unusual and dramatic side effect from IV pethidine administration and its implications.

Keywords: Pethidine, Intravenous, Histamine, Adverse effect, Side effect

Abbreviations: ECG- electrocardiogram, BMI- body mass index, SSRI- selective serotonin reuptake inhibitors, MAO inhibitors- monoamine oxidase inhibitors, IV- intravenous, ASA- American Society of Anesthesiologists.

Case
A 41 year old female patient (ASA II) underwent an incision and drainage of her perianal abscess under a general anaesthetic as an urgent procedure. She was known to have anorexia nervosa and was under medical management for it. She had a BMI of 18.5. She also suffered from eczema and mild asthma. She gave a history of irregular heart rhythm in the past. She had a normal ECG and echocardiogram. She was on fluoxetine, salbutamol inhaler, beclometasone inhaler and ricatriptan. She had normal blood investigations prior to induction.

Her anaesthetic was induced with propofol and fentanyl and was maintained on oxygen/air/sevoflurane. She was on spontaneous ventilation through a laryngeal mask. She also received paracetamol and ondansetron intraoperatively. She was haemodynamically stable during the twenty minute procedure, which was done in the lateral position.

The laryngeal mask came out ten minutes after her arrival in recovery. The patient asked for pain relief ten minutes after waking up. IV pethidine 25mg (diluted to 12.5 mg/ml) was given by the recovery nurse who, within five minutes, noted severe redness in the distribution of the vein into which it was injected (Figure 1). The anaesthetist was notified, who then flushed the IV line with normal saline. The redness settled down within 15-20 minutes of the start of the reaction (Figure 2 to 4). The patient was haemodynamically stable and didn’t complain of any local or systemic symptoms.

Discussion
Pethidine has been known to release histamine on systemic administration1. It can also have interactions with various drug groups like SSRIs and MAO inhibitors to cause serotonin syndrome2,3 and can present with tachycardia, hypertension, hyperthermia, agitation and even seizures, among other signs and symptoms. Pethidine is equipotent to morphine and codeine in terms of histamine release 4.

This case is most likely due to profound histamine release in a patient with atopic tendency. The factors thought to increase the incidence and severity of this reaction are 5:

- Old age
- Thin body structure
- Poor peripheral circulation
- Volar > dorsal veins
- Repeated injection into the same superficial vein
- High concentration of solution of injection (>10 mg/ml solution)

The factors that have no influence are:

- Pretreatment with an antihistamine
- History of previous pethidine use
- Using pethidine as a premedication

In the past, diluting pethidine with 0.25% procaine also provided protection against the reaction.

There were no other signs of serotonin excess in this patient and she came to no harm. The presentation was dramatic enough to cause concern but was self-limiting.

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Competing Interests
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2. BNF, November 2013
An aggressive follicular variant of papillary thyroid carcinoma with unusual metastases - A case report and review of literature

Isaac Sachmechi, Rachelle N Bitton, Susan Sanelli-Russo and Supat Thongpooswan

Abstract
Metastatic carcinoma to the sinonasal tract is rare, by papillary thyroid cancer even rarer. We describe a 44-year-old Hispanic woman with follicular variant papillary thyroid carcinoma treated with total thyroidectomy and post-surgery 131I ablation. Post therapy, two consecutive body scans were negative and thyroglobulin level was less than 5 ng/ml. A year later, she presented with history of urinary retention and lower extremity weakness. A myelogram revealed block at T1-T2. Patient underwent laminectomy followed by external radiation. Pathology revealed metastatic follicular variant of papillary thyroid carcinoma. Total body scan post-surgery was negative, and the thyroglobulin level was 5 ng/ml. Patient was maintained on thyroxine suppression therapy. Two years later, patient started complaining of headaches and double vision. Magnetic resonance imaging (MRI) was done and revealed a soft tissue mass in the sphenoid sinus, eroding the basisphenoid and extending into the nasopharynx. Biopsy was positive for metastatic papillary thyroid cancer, follicular variant. Pituitary function testing revealed TSH 0.1 mIU/ml, free T4 level 1.2 mIU/ml, AM cortisol 5.3 mcg/dl, prolactin 182 ng/ml, ACTH 12 pg/ml, FSH 11.5 mIU/ml, LH 4.0 mIU/ml, and Estradiol 20 pg/ml. Metastasis to the sphenoid sinus is rare from any tumour, and from papillary thyroid cancer is extremely rare. An extensive world literature review revealed only 4 cases of papillary thyroid carcinoma with spread to sphenoid sinus region. Of 12 case reports of thyroid carcinoma with spread to the sphenoid sinus, 6 were follicular thyroid carcinoma. Generally, total body scan negative with low stimulated thyroglobulin is an excellent prognostic sign. Our patient demonstrates that we need to remain vigilant for the unusual tumour especially when the initial presentation showed a large lesion.

Keywords: papillary thyroid carcinoma, metastasis, sphenoid sinus

Abbreviations: MRI- Magnetic resonance imaging TSH- Thyroid stimulating hormone PET- positron emission tomography CT- computerized tomography

Introduction
Metastatic carcinoma to the sinonasal tract is rare. We describe a patient with an aggressive follicular variant of papillary thyroid carcinoma who presented with an unusual metastasis to sphenoid sinus.

Case report
A 44 year old Hispanic woman presented at Queens Hospital Center in June 1988 with airway obstruction and was found to have a 10x12 cm firm mass in the left thyroid lobe, and palpable left supraclavicular node. She had no prior history of radiation, and no family of thyroid cancer. She underwent a total thyroidectomy with a modified radical neck dissection. Pathology revealed a follicular variant of papillary thyroid carcinoma: non-tall cell variant. Six of fifty (6/50) lymph nodes were positive. Post-surgery, patient received Iodine-131 ablation therapy (93 mCi) and was placed on thyroid hormone suppressive therapy. Non-stimulated thyroglobin total body scan a week after therapy was negative. Thyroglobin was not available at that time.

The patient was non-compliant with thyroxine and thyroid stimulating hormone (TSH) was often elevated (13-80 mIU/ml). However, the serum thyroglobulin remained less than 5.0 ng/ml and antithyroglobulin antibody was negative. A repeat total body scan (with 5 mCi 131I) 6 months later and 4 years later with thyroxin withdrawal (TSH 36 mIU/ml and 48 mIU/ml respectively) was negative, and patient was continued on thyroxine suppression therapy.

Five years after initial presentation, the patient developed urinary retention and lower extremity weakness. A myelogram revealed block at T1-T2. Patient underwent laminectomy. Pathology revealed metastatic follicular variant of papillary thyroid carcinoma. Since iodine containing contrast was used during the myelogram, 131I iodine therapy was not given. External radiation of 2000 CGY to C7-T5 was administered.

A total body scan 8 weeks post laminectomy (when 24 hour urine iodine < 100 microgram/litre, and TSH was 38 mIU/ml after thyroid hormone withdrawal) was negative, the thyroglobulin level was 5 ng/ml and negative antithyroglobulin antibody (at that period of time, positron emission tomography (PET) scan was not an available option). For the next 2 years of follow up, the patient was maintained on thyroxin suppression therapy, this time with good compliance (TSH 0.1 mIU/ml, thyroglobulin less than 5 ng/ml and negative antithyroglobulin antibody). She did not show up for follow up lumbar computerised tomography (CT).
Figure 1: A-T1 weighted midline sagittal MRI scan without contrast. B-T1 weighted midline sagittal MRI scan with contrast. C-T2 weighted axial MRI scan through the lesion. D-Axial CT scans without (on the left) and with (on the right) contrast. Note: The large destructive and enhancing lesion (*) in the sphenoid sinus associated with destruction of the basisphenoid, clivus and sellar floor. Note the normal pituitary gland (arrow) is displaced upwards out the sellatubtus.

Table 1: Cases of thyroid metastases to the sphenoid sinus

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Presenting symptoms</th>
<th>Histologic type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present case</td>
<td>44</td>
<td>F</td>
<td>Headache, double vision and amenorrhea</td>
<td>Follicular variant papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Mandronio (2011)</td>
<td>53</td>
<td>F</td>
<td>Blurring of vision of left eye</td>
<td>Papillary metastatic thyroid carcinoma</td>
</tr>
<tr>
<td>Nishijima (2010)</td>
<td>81</td>
<td>F</td>
<td>Epistaxis</td>
<td>Differentiated papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Argibay Vasquez (2005)</td>
<td>53</td>
<td>F</td>
<td>Headache, paresthesia in the right eye region and left monocular diplopia</td>
<td>Differentiated carcinoma of thyroid, follicular variant of papillary cell</td>
</tr>
<tr>
<td>Altman (1997)</td>
<td>81</td>
<td>F</td>
<td>Progressive headache</td>
<td>Follicular thyroid carcinoma</td>
</tr>
<tr>
<td>Freeman (1996)</td>
<td>50</td>
<td>M</td>
<td>Facial pain, proptosis of the left globe and left horner’s syndrome</td>
<td>Metastatic papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Yamatosoba (1994)</td>
<td>34</td>
<td>F</td>
<td>Hearing loss in right ear</td>
<td>Follicular thyroid carcinoma</td>
</tr>
<tr>
<td>Cumberworth (1994)</td>
<td>62</td>
<td>F</td>
<td>Right nasal blockage</td>
<td>Follicular carcinoma of the thyroid</td>
</tr>
<tr>
<td>Renner (1984)</td>
<td>61</td>
<td>F</td>
<td>Profuse right unilateral epistaxis</td>
<td>Follicular thyroid adenocarcinoma</td>
</tr>
<tr>
<td>Chang (1983)</td>
<td>50</td>
<td>F</td>
<td>Intermittent epistaxis, weight loss and pain in the right nasopharyngeal region</td>
<td>Follicular carcinoma with papillary foci</td>
</tr>
<tr>
<td>Barrs (1979)</td>
<td>54</td>
<td>F</td>
<td>Progressive loss of vision in the left eye</td>
<td>Follicular thyroid carcinoma</td>
</tr>
<tr>
<td>Harmer (1899)</td>
<td>44</td>
<td>F</td>
<td>Headache</td>
<td>Medullary thyroid carcinoma</td>
</tr>
<tr>
<td>von Eiselsberg (1893)</td>
<td>38</td>
<td>M</td>
<td>Chronic meningitis</td>
<td>Thyroid carcinoma</td>
</tr>
</tbody>
</table>
Seven years after the initial presentation, she complained of headache and double vision, and a three month history of amenorrhea. The thyroglobulin at this time was elevated (20 ng/ml). Chest X-ray was positive for two nodules in the right lung. Magnetic resonance imaging (MRI) revealed a soft tissue mass in the sphenoid sinus, eroding the basi-sphenoid and extending into the nasopharynx (Fig. 1 ABCD). The mass also eroded the sella floor displacing the pituitary gland upwards (arrows). Bone scan revealed focal abnormalities in the upper thoracic spine, ethmoid bones and base of the skull. At that period of time, PET scan was not an available option. Pituitary function testing revealed TSH 0.1 mIU/ml, free T4 level 1.2 mIU/ml. AM cortisol 5.3 mcg/dl, prolactin 182 ng/ml, ACTH 12 pg/ml, FSH 11.5 mIU/ml, LH 4.0 mIU/ml, and Estradiol 20 pg/ml.

Biopsy of the sphenoid sinus mass confirmed that it was metastatic papillary thyroid cancer, follicular variant. The tumour cell nuclear DNA was diploid and P53 and K167 were negative (Impat, NY). The patient was placed on hydrocortisone replacement and continued on thyroxine suppression therapy. Three months later the patient suffered a cardiorespiratory arrest and expired.

Discussion

Metastasis to the sphenoid sinus is rare from any tumour, and from papillary thyroid cancer it is extremely rare. An extensive world literature review revealed only 4 cases of spread to sphenoid sinus region from papillary thyroid cancer. 1-4

Renal cell carcinoma is the most common tumour of paranasal sinus metastasis, 41.8%. The average age is 58 years, with slight predominance of males. The most common presentation was epistaxis, 31%. The most common causes of sphenoid sinus metastasis are gastrointestinal and renal tumours. 5

Von Eiselsberg et al. in 1893 described one case of metastasising thyroid carcinoma to sphenoid sinus. 6 Harmer et al., 1899, reported a case of medullary thyroid carcinoma metastasis to sphenoid/ ethmoid sinus and nose. 7 Barrs et al. in 1979 reported a case of metastasis of follicular thyroid carcinoma to sphenoid sinus and sphenoid bone. 8 Chang et al. in 1983 described a case of metastatic carcinoma of the thyroid to the sphenoid sinus. 9 Renners et al. in 1992 reported one case of metastasis of follicular thyroid carcinoma to the paranasal sinuses, including the sphenoid sinus. 10 Yamasoba et al. in 1994 reported a case with follicular thyroid carcinoma metastasising to sinonasal tract which also included sphenoid sinus. 11 In the same year, Cumberworth et al. reported a case of metastasis of a thyroid follicular carcinoma to the sinonasal cavity which head CT showed sphenoid, ethmoid, frontal and maxillary sinuses. 12 In 1997, Altman et al. described a case of follicular metastatic thyroid carcinoma to paranasal sinuses which included the sphenoid sinus. 13 The reported cases of thyroid cancer metastasis to sphenoid sinus are in table 1. Four cases were papillary thyroid carcinoma (included follicular variant of papillary thyroid carcinoma), six cases were follicular thyroid carcinoma, 1 case was medullary thyroid carcinoma and 1 case was unspecified thyroid carcinoma.

Pathologic lesions involving the sphenoid sinus include inflammatory disease, mucocele, chordoma, nasopharyngeal carcinoma, plasmacytoma, primary sphenoid sinus carcinoma, adenocystic carcinoma, pituitary adenoma, and giant cell granuloma. Benign disease often presents with a more gradual obstruction and disturbance of vision. This contrasts with the acute and progressive disturbances of vision in all cases reported with malignant lesions of the sphenoid sinus. 14

Our patient presented with complaints of double vision for 6 months and headache. After imaging with MRI and given her previous history of metastatic thyroid cancer, the most likely diagnosis was metastases to the sphenoid sinus from the thyroid cancer, which was confirmed by tissue biopsy. Since this patient had evidence of bone metastasis, it is likely that the tumour first metastasised to the bone and then ruptured into the sphenoid sinus. The tumour appears to have eroded the sellar floor, extending into and displacing the pituitary gland, causing secondary hypoadrenalism.

In our patient, low thyroglobulin proved to be an unreliable marker because it was low when the patient had metastasis of the tumour in the spine. These tumours are more aggressive and today, PET scanning has proved more reliable in following them, a modality that was not available at the time for our patient. The possible explanations for negative total body scans in patients with metastatic differentiated thyroid cancer are a) technical limitations of the scan in detecting the tumour cells, and b) failure of the tumour tissue to trap iodine.

There are several unusual aspects in this patient’s presentation. Firstly, the initial presentation was unusual, since this tumour was very aggressive with rare sites of distant metastases. Perhaps the long periods of hypothyroidism when patient was noncompliant promoted the aggressive nature of this tumour. Secondly, the failure of known tumour markers, i.e. serum thyroglobulin and total body scan to identify these metastases. Thirdly, our patient’s tumour cell nuclear DNA was diploid. Investigations have shown that the DNA ploidy pattern as determined by flow cytometry is an important and independent prognostic variable. 15-17 Fortunately, aggressive follicular variant papillary cancer of thyroid (non-tall cell type) is very uncommon.

Generally, total body scan negative with low stimulated thyroglobulin is an excellent prognostic sign. Our patient demonstrates that we need to remain vigilant for the unusual tumour especially when the initial presentation showed so much bulky disease. The need for additional tumour markers will help to identify aggressive well differentiated thyroid carcinoma cases.
Acknowledgement

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Competing Interests

None declared

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REFERENCES


Patellar fracture fixation: An unreported complication occurring directly attributable to tension band fixation of the patella.

Peter Alexander Gilmer Torrie, James, Smith and Michael Kelly.

Abstract
Patella fractures account for 1% of all fractures but there is little in the contemporary literature regarding either an optimal standardized post-operative rehabilitation regimen or the long-term outcomes following these fractures. Tension band wire fixation for displaced patella fractures is a well-recognized and accepted method of operative treatment for these fractures. In this case the authors report a new complication, yet to be documented in the literature that was directly attributable to a well-recognized complication resulting from this method of fixation. An atypical osteochondral defect, from the lateral femoral condyle, was generated as a direct result of bony spur at the site of the previous patella fracture malunion. As the patient fell on to her knee the bony spur was driven into the femoral condyle in a similar fashion to an osteotome, generating the atypical osteochondral defect.

This patient had chronic anterior knee pain following the tension band fixation of her patella. An inadequate standardized follow-up regimen failed to identify her fracture malunion that was responsible for her ongoing persistent symptoms. Only as a result of this previously unreported complication, we were able to identify and surgically address the underlying primary pathology responsible for her persistent symptoms. This case highlights the importance for the identification and establishment of a more robust imaging follow-up regimen post patella fracture fixation.

Keywords: patella fracture; tension band fixation; unreported complication; post-operative follow-up regimen

Introduction

Patella fractures account for 1% of all fractures but there is little in the contemporary literature regarding outcomes. It is accepted that where fixation is required it needs to be rigid and tension band wiring using cannulated screws or k-wires is the accepted standard. Recognised complications associated with this form of fixation occur in up to 15% of cases and include; infection, loss of fixation, knee stiffness, post-traumatic osteoarthritis, malunion, nonunion and irritation from hardware. There is nothing in the literature regarding the natural history following fixation.

We report an unusual complication of an osteochondral defect being generated as a direct result of a malunion of a patella fracture previously fixed by a tension band wiring technique.

Case Report
A 35-year old lady presented to our unit after a direct fall on to her left knee with an associated dislocation of her patella that spontaneously reduced on extension, at the time of injury. Three years previously she had sustained a patella fracture that had been treated with tension band wiring. From the time of the original fixation she had experienced mild persistent anterior knee pain, with a reduced range of motion and grinding. She had been discharged from further follow up.

On this presentation, examination revealed that she had a marked knee effusion with a functional extensor mechanism and a range of motion from 0-60 degrees.

The initial radiographs demonstrated that she had broken hardware and an incongruency of the patella suggesting malunion on the articular surface with a residual step (figure 1). In addition, an osteochondral fragment was identified in the patellofemoral joint. Computer tomography was undertaken and confirmed the osteochondral fragment had come from the lateral femoral condyle and a spur like prominence on the articular surface of the patella (figure 2). The mechanism was that this bony spur had been driven into the articular surface of the lateral condyle on dislocation resulting in the osteochondral fragment being generated.

Intraoperative findings confirmed this and measured the osteochondral fragment as 40x15mm (figure 3). In addition it was found that the lateral longitudinal wire had protruded into the joint causing a vertical linear defect in the articular surface of the trochlea.

The osteochondral defect was reduced and stabilized with interrupted 3/0 PDS sutures achieving a smooth articular surface (figure 4). In addition a patelloplasty and a lateral release were performed to remove the bony prominence and restore patella tracking respectively. At 6-month follow up this patient was progressing well with rehabilitation and the majority of her chronic symptoms had resolved.
Figure 1. Lateral radiograph demonstrating an incongruency of the patella suggesting malunion on the articular surface with a residual step.

Figure 2. Computerised Tomography confirming an osteochondral fragment that had come from the lateral femoral condyle.

Figure 3. Osteochondral fragment from the lateral femoral condyle measuring 40x15mm.

Figure 4. The osteochondral defect stabilized with interrupted 3/0 PDS sutures achieving a smooth articular surface.

Discussion

Although patellae account for 1% of fractures their functional outcome remains largely ignored in the literature. This case presents an unreported complication and highlights that symptoms can remain following the initial fixation that are accepted either by the patient or the treating centre and not further investigated.

Osteoarthritis of the knee remains the most common musculoskeletal complaint in general practice but even then only a third of those with symptoms seek medical advice. Therefore the lack of re-referrals following fixation is not an accurate way to assess outcome following patella fractures treated with this mode of fixation.

Patella fractures represent only a small number of fractures and therefore assessment of treatment and outcomes is problematic, particularly as there is no standardised rehabilitation regimen.

We report on this case as it illustrates a complication of patella fracture fixation that has not been previously described or routinely recognised and, additionally, highlights the fundamental importance of a comprehensive standardised post-operative imaging follow-up regimen. It may be that patients are not currently being correctly counselled regarding the longer-term expectations following patella fracture. A study to define the natural history of patella fractures following contemporary management is needed.

Competing Interests
None declared

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Self-induced burn injury from thermal footbath in patients with diabetes neuropathy—a common mishap in Asian culture

Huai Heng Loh and Florence Tan

Abstract

We report three cases of diabetic patients with peripheral neuropathy who sustained severe burn injuries to the foot due to use of thermal footbath with the intention to "improve circulation" and "relieve numbness". Use of thermal footbath is common among Asian diabetic patients with peripheral neuropathy. This has resulted in accidental burn injuries. Due to high susceptibility to secondary infection, delayed presentation further complicates and prolongs hospital stay. There is a need for greater public awareness. Education regarding avoidance and consequences of this highly preventable injury should be incorporated into standard diabetic foot care education in clinical practice.

Keywords: Thermal footbath, severe burn injuries, diabetic neuropathy

Introduction

Diabetic patients with peripheral neuropathy are predisposed to foot injury. In Asian countries, a common culture among patients with peripheral neuropathy is to immerse their feet in hot water baths, with a belief that it will "improve circulation" and hence "cure the numbness". We hereby report three cases of severe burn injuries of the feet presented to our hospital over a span of six months due to the above belief.

Case Report

The first patient was a 53-year old Malay gentleman with poorly controlled diabetes mellitus for six years, complicated with peripheral neuropathy, diabetic nephropathy and right eye cataract (latest HbA1C 8.1%), treated with oral anti-diabetic agents. He had a habit of using hot footbaths for numbness of both feet. Two weeks prior to presentation, due to increased feeling of numbness, he immersed his right foot into a self-prepared tub of hot water with added salt, followed by application of traditional sea cucumber gel. That evening, he noticed blistering of his right foot. Despite advice for admission, he chose to do the dressing as an outpatient in a local clinic. He presented two weeks later due to a worsening wound. At presentation, 4% full thickness burn of his right foot was noted, complicated by secondary infection (Figure 1). He underwent wound debridement, and subsequent split skin grafting. He had a prolonged hospitalization of five weeks due to secondary pseudomonas wound infection requiring parenteral antibiotics.

The second patient was a 26-year old Indian gentleman with type I diabetes mellitus for nine years, complicated with diabetic nephropathy and peripheral neuropathy. His wife usually prepared hot water footbaths for him to improve his feet circulation. He developed 5% full thickness burn when he immersed his right foot into a pail of boiling water, not knowing that his wife had not added cold water into the footbath. He presented himself after two days and was hospitalized for two weeks. He recovered after wound debridement and split skin grafting.

The third patient was a 17-year old Chinese lady with poorly controlled type I diabetes mellitus for eight years, complicated with diabetic nephropathy (latest HbA1C 10.0%). She used hot water steam therapy with an aim to cure her recent onset of left foot drop, but was unaware of the temperature of the water. She developed blisters on her left foot, but only presented herself two weeks later when she developed left foot gas gangrene. She had a prolonged hospital stay of eight weeks with recurrent hospital acquired infections, including Methicillin-resistant Staphylococcus aureus (MRSA). Despite multiple wound debridement, she required amputation of her left fifth toe (Figure 2).
Peripheral neuropathy is a known complication of diabetes mellitus. More than 50% of patients who are over 60 years old have this complication.\(^1,2\) Thermal injury to the feet in patients with neuropathy has been reported after walking barefoot on hot surfaces\(^3\) and after application of hot water bottles or heating pads during winter months.\(^4,5\) The use of thermal footbath as a cause of burn injury is mostly due to patient-misuse or ignorance of correct usage.\(^6,7\) In contrast, in Asian countries, a common culture among patients with peripheral neuropathy is to immerse their feet in self-prepared hot water without checking the water temperature,\(^8\) with a belief that it will “improve circulation” and hence “cure the numbness”. This practice has led to accidental burn injuries as described in our case reports.

There are a few reasons why patients with diabetic peripheral neuropathy end up with such a severe complication after the use of thermal footbath. Firstly, the temperature of the thermal bath may be underestimated. The time to develop full thickness burn reduces exponentially with just minimal increments in water temperature.\(^9\) Secondly, lack of pain despite the burn can prolong exposure to the heat source. In addition, concomitant peripheral vascular disease and endothelial function can limit vasodilatation to conduct heat away hence further aggravate the thermal insult.

Another important contributing factor of complicated wounds are the delays in seeking treatment as the result of lack of pain despite the burn injury. In a study done by Memmel et al on 1794 patients (of which 130 were diabetics) who presented with burn injuries, the majority of non-diabetic burn patients (63%) presented within 48 hours of injury, but only 40% of diabetic patients sought treatment within that time frame. Significantly more patients with diabetes presented after two weeks compared to those without diabetes. As burn injuries are highly susceptible to secondary infection, any delay in presentation further complicates and prolongs hospital stay.\(^10,11\) Not surprisingly, our two patients who presented two weeks after their burn injury had a prolonged and complicated hospital course compared to our second patient who presented soon after the burn injury. Increased susceptibility to infection and delayed wound healing from poor circulation contribute to prolonged recovery and poorer clinical outcomes in patients with diabetes mellitus, with some needing amputation as noted in our third patient.

As a healthcare provider we play a role in preventing this misfortune. Routine screening for the presence of peripheral neuropathy and vascular disease should be done during clinic visits to identify high-risk patients. Specific education regarding avoidance of thermal footbath and consequences of this highly preventable injury should be incorporated into standard diabetic foot care education. If patients choose to immerse their feet in hot water, temperature of the water should always be measured with a thermometer and immersion time should be limited. If a wound develops, they should present early to hospital for immediate treatment.

Conclusion

Thermal footbath for therapeutic purposes is commonly practiced in Asian culture. Our case reports highlight the serious consequences of this practice in diabetic patients with peripheral neuropathy. More public awareness and patient education is needed to prevent these injuries and to avoid the high cost of prolonged hospital stay and losses to the patient.

Competing Interests
None declared

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A 32-year old female with medical history of Diabetes Mellitus (type 2) presents to the outpatient clinic with a 2-day history of pain in the roof of her mouth. She described the pain as severe, throbbing, non-radiating, and unrelieved by analgesics. Fever was absent and there were no symptoms suggestive of an antecedent respiratory tract infection (RTI). She had no history of oral mucosa trauma or burns. She gave a remote history of herpes oralis and aphthous ulcers. Her diabetes is well controlled with Sitagliptan-Metformin and Lantus. An annual dental examination done in the past year was described as “normal” by the patient. She maintains oral hygiene with daily teeth brushing without flossing; she had never used dentures. Further review of systems was negative. On examination she was not in distress and vital signs were normal. No external orofacial or neck swelling was observed. Oral examination revealed dental plaques and periodontal lesions. A 2x2cm tender paramedian mass with a small central ulcer was seen and felt on the hard palate anteriorly (see Figure 1 and 2). There were no pharyngotonsillar lesions or regional lymphadenopathy. Tongue and deglutitive movements were normal. Systemic examination was normal. STD/HIV screening was negative. The clinical picture is most consistent with:

- Torus palatinus with aphthous ulceration
- Hyperplastic candidiasis
- Palatal pleomorphic adenoma
- Median palatine cyst
- Palatal abscess
The clinical picture is most consistent with a palatal abscess. Palatal abscess is a pyogenic collection representing a palatally directed drainage of infective pulpal, pericoronal or periodontal process. The most common origin is from an infection of the palatal root of maxillary premolars or molars. It presents as a very painful, fluctuant swelling, with lateral or paramedian localization. The surrounding edema may give an impression of midline involvement or contralateral extension. The prevailing dental plaques and periodontitis present in this patient (her diabetic state abetting), creates a rich source of oral aerobes and anaerobes as well as the environment in which they thrive. An antecedent herpetic or aphthous ulcer may also be portal of entry for causative microbes. The patient’s oral hygiene status, her diabetic state, the acuity of symptoms and markedly painful presentation are consistent with acute palatal abscess. The absence of fever in this patient does not preclude this diagnosis.

Hyperplastic candidiasis is the result of chronic colonization and superficial oral mucosa invasion by Candida sp, causing chronic inflammatory changes with edema and epithelial proliferation. The result of these reactive responses is a raised pebbled-like surfaced lesion. It is most commonly seen under denture sites in denture wearers. The lesion depicted in the picture above is not typical for hyperplastic candidiasis, more so, though not an absolute discriminant, the patient had never used dentures.

Torus palatinus is a wide-based, smooth surfaced, bony protrusion in midline of the hard palate caused by cortical bone growth with a thin, poorly vascularized mucosa lining. The etiology is unclear, but is thought to be multifactorial; genetics (autosomal dominant trait) and recurrent superficial palatal injuries most often implicated. Torus palatinus is often an incidental finding, though some affected persons may present out of concern for its increasing size or interval development of ulceration or pain in the area of the torus. Pleomorphic adenoma is the most common neoplasm of salivary glands. Though it may occur at any age, pleomorphic adenoma of salivary glands has peak incidence in the fourth to sixth decade of life. Palatal pleomorphic adenoma often presents as a painless, slow-growing tumor. Median palatine cyst is a rare, non-odontogenic lesion of the hard palate that usually presents as a painless, fluctuant swelling. They are composed histologically of a fibrous collagenous tissue wall, with infiltration of chronic inflammatory cells, and lined by stratified squamous and/or respiratory epithelium. Pain is unusual in the above three oral diagnostic entities, when present it arises from ulcerative, hemorrhagic or infective complications. A detailed history eliciting the chronicity of a preceding midline palatal swelling is often helpful. The patient reported normal palatal examination a year earlier, the relative short history, and the acuity of presentation (severity of pain) make torus palatinus, median palatine cyst or palatal pleomorphic adenoma unlikely. See Table 1 for discriminants and differential diagnoses.

Table 1: Differential Diagnoses of Palatal Swelling

<table>
<thead>
<tr>
<th>Onset and course</th>
<th>Palatal abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>Torus palatinus, median palatal cyst, pleomorphic adenoma, hyperplastic candidiasis</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
</tr>
<tr>
<td>Globular</td>
<td>Palatal abscess, torus palatinus, median palatal cyst, pleomorphic adenoma</td>
</tr>
<tr>
<td>Peppled</td>
<td>Hyperplastic candidiasis</td>
</tr>
<tr>
<td>Consistency</td>
<td></td>
</tr>
<tr>
<td>Fluctuant/tense</td>
<td>Palatal abscess, median palatal cyst</td>
</tr>
<tr>
<td>Rubbery/firm</td>
<td>Torus palatinus, pleomorphic adenoma, hyperplastic candidiasis</td>
</tr>
<tr>
<td>Associated pain</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Palatal abscess, hyperplastic candidiasis, infective or traumatic complications of: torus palatinus, median palatal cyst, pleomorphic adenoma</td>
</tr>
<tr>
<td>No</td>
<td>Uncomplicated: torus palatinus, median palatal cyst, pleomorphic adenoma</td>
</tr>
<tr>
<td>Associated fever</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Palatal abscess (but may not be present)</td>
</tr>
<tr>
<td>No</td>
<td>Hyperplastic candidiasis, uncomplicated: torus palatinus, median palatal cyst, pleomorphic adenoma</td>
</tr>
<tr>
<td>Patient attributes</td>
<td></td>
</tr>
<tr>
<td>Poor oral hygiene/caries</td>
<td>Palatal abscess</td>
</tr>
<tr>
<td>Diabetes/HIV</td>
<td>Palatal abscess</td>
</tr>
<tr>
<td>Denture wearer</td>
<td>Hyperplastic candidiasis</td>
</tr>
</tbody>
</table>

The patient underwent definitive treatment with incision and drainage of abscess as well as extraction of her upper left second molar by a dental surgeon. She completed a course of Clindamycin as well as multiple scaling and polishing sessions by a dental hygienist. Maintaining oral hygiene by daily teeth brushing, and flossing, use of mouth antiseptic, as well as a biannual visit to her dentist was recommended.
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“Of the depression” - A Poem by Dr Javed Latoo

When aquamarine skies look grey to our eyes
   The stars no longer adorn the heavens or shine bright;
When the golden rays of sunlight disappear from the skies
   The silver rays of the moonlight look like phantoms of the night.

When we feel imprisoned with no escape from this dark place
   And dazzling beauty looks like an old wrinkled face;
When sorrowful eyes stare into a cold empty space
   Oblivious of the beauty displayed on our loved one’s face.

In this period we are neglected by the angel of sleep
   The taste of our favourite food is appetising no more;
When we are drained of the sap of life and tend to weep
   And the brain cannot concentrate anymore.

That state when the mind tricks us to believe we are worthless
   The heart is eaten by the bug of guilt over the trivialness;
When we are overwhelmed by hopelessness
   All consolations about the future seem only fruitless.

When we no longer enjoy the company of our loved ones
   Isolate from the things we would normally enjoy;
Overwhelmed by the feelings of being down in the dumps, once
   Minor bumps become boulders difficult to navigate and destroy.

When our minds ruminate about the past and future, furthermore
   Reassurances don’t dampen the worrying cognition;
When life does not seem to be worth living anymore
   And we start getting fleeting suicidal ideation.

Remember that this dark cloud of despair we feel
   Is an ailment called depression and not a curse; and be aware
It is a transitory period rather than an everlasting phase or ordeal
   Treatment and recovery are available from the experts who care.

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