KHARTOUM
MEDICAL JOURNAL
The Official Journal of the Faculty of Medicine, University of Khartoum
**Published every four months**



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ISSN 1858-5345

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6. Act as a platform for the expression of professional and scientific opinion and exchange of information.
7. Provide a forum for the exchange of ideas and experiences in the field of education and training in the medical and health professions.

# Contents

# Review

## Surgical management of renal cell carcinoma

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## Background

**Renal Cell carcinomas**(adenocarcinoma of the renal cortex) originate from the proximal renal tubular epithelium.(1) This was thought to originate from adrenal gland hence the previous misnomer ***Hypernephroma,*** also known as ***Grawitz tumor*** and ***Clear Cell Carcinoma.***(1, 2)

In the United States approximately 58,000 cases were diagnosed in 2010 with a subsequent 44% mortality. In the European Union 84,400 cases were diagnosed in 2012; of these there were 34,000 (40%) related deaths. RCC has a male predominance with a male to female ratio of 1.5-2:1.(1-3)

Multiple etiological factors have been implicated in the pathogenesis of renal cell carcinoma. These include: smoking, obesity, hypertension and non-aspirin non- steroidal anti inflammatory drugs. Other factors include acquired polycystic kidney disease.(1-3)

Genetic predisposition to renal cell carcinoma has been identified. 50% of individuals with Von Hippel Lindau syndrome develop RCC. Individuals with papillary RCC and Birt-Hogg-Dube syndrome have been identified among others.(1)

### Pathology and Staging

Histologically RCC is a mixed adenocarcinoma containing clear cells, granular cells and less frequently sarcomatoid cells. These are classified into subtypes including: clear cell (80%), papillary (10-15%), chromophobe (5%), collecting duct (5%) or medullary cell.(2)

Renal tumors are staged utilizing 2009 TNM classification system (supplemented in 2012). Survival for RCC is determined by TNM stage, pathological grade, performance status and molecular factors (VEGF, HIF-1).(2, 3)

### Staging

Renal tumors are staged according to the 2009 TNM classification system from T1 to T4 according to their size and invasion of adjacent structures: tumors less than 7cms are T1; tumors 7cms or larger are T2 only if confined to the kidney. T3 tumors are tumors extending into Gerota's fascia and/ or involving the great vessels including the inferior vena cava below or above the diaphragm. T4 includes any tumor extending into the ipsilateral adrenal gland or extending beyond Gerota's fascia. The presence of nodal or distal metastasis is labeled N1, M1 respectively.(3)

### Diagnosis

Currently up to 50% of renal tumors are incidentally diagnosed. However, only 10% of patients present with the classic triad of haematuria, flank pain and flank mass. Another 30% of patients present with symptoms of metastatic disease (lung, bone, liver or brain). Para-neoplastic syndromes associated with renal cell carcinomas include: anaemia; polycythaemia; hypertension; cushing's syndrome; and hypercalcaemia.(2, 3)

CT scan or MRI scan accurately diagnose renal masses. Presence of enhancement on administration of contrast differentiates malignant lesions. Additional information obtained include: tumor extent; function of contralateral kidney ; and involvement of lymph nodes, renal vein, vena cava

and adrenal gland. Chest radiographs are performed interchangeably with CT scans although being less accurate. However, routine bone and brain scans are not performed unless other symptoms of metastasis are present.[2, 3]

## Surgical Treatment

Surgical treatment (radical nephrectomy) is the only curative treatment for localized renal tumors (T1-T2 N0M0) with a preference of partial nephrectomy for tumors up to 7 centimeters.[4]

Radical nephrectomy entails en bloc resection of the kidney with perinephric fat, the ipsilateral adrenal gland and the regional lymph nodes: para-aortic from the bifurcation of the aorta to the crus of the diaphragm plus para-caval nodes. Access can be achieved retroperitoneally, transperitoneally or through thoraco -abdominal incisions. Whereas partial nephrectomy (nephron sparing surgery-NSS) involves resection of the renal mass with a rim of normal renal tissue, achieved under temporary control of the renal vasculature thence enucleation, wedge excision or, extremely rarely, extracorporeal resection followed by auto transplantation. Effective closure of the collecting system should be attained. [5]

Partial nephrectomy was initially reserved for patients with bilateral renal tumors; solitary functioning kidneys; syndromes predisposing to recurrence or multiple tumors. Additional indications include : contralateral renal artery stenosis; hydronephrosis; chronic pyelonephritis; and systemic disease affecting the kidney function. However, this is now considered the standard treatment for renal tumors 4 cms or less in size in most of the urological guidelines.[4-6]

## Radical versus Partial Nephrectomy

Van Poppel et al, in a randomized multicenter study conducted by the European Organization for Research and Treatment of Cancer Genito-Urinary (EORTC –GU) group, compared radical nephrectomy to partial nephrectomy in patients with T1 tumors 5cms or less in size. The study involved 273 patients and 268 patients for the respective study arms. Surgical complications including :arteriovenous fistulae; perioperative bleeding and pleural injuries were all higher in the partial nephrectomy group. However, after a median duration of 9.3 years of follow- up, 25% of partial nephrectomy and 18.3% of radical nephrectomy had died from multiple causes: cardiovascular disease was the cause in 9.3% and 7.3% in the respective groups. Cancer- related death was seen in 8 partial and 4 radical nephrectomy patients which were not statistically significant. Another important point was cancer progression which was seen in 4.1% and 3.3% for the respective partial and radical nephrectomy groups. The difference was not statistically significant.[7]

Similarly, Lau et al, performed a matched- case analysis and found no difference in overall survival, 10 year survival and cancer specific survival when comparing the 2 groups of patients.[8] On the other hand, Roos et al in a retrospective analysis of 4326 patients found that both elective and imperative partial nephrectomy were associated with higher overall 5 year survival as compared to patients who received radical nephrectomy at (90%) for elective partial nephrectomy, (83.9%) imperative partial and (81.2%) for radical nephrectomy patients.[9] Tan et al, compared both procedures in a cohort of 7,138 patients and found that patients who received partial nephrectomy (27%) had a lower overall and cancer -specific mortality, and on a predictive model they found that the same group had an improved predicted survival at 2, 5 and 8 years of 5.6%,11.8% and 15.5%.[10] Borregales et al, on analyzing long-term renal functions, found that partial nephrectomy was associated with longer overall survival.[11]

Huang et al, evaluated 2991 patients who underwent surgery for renal masses 4 cms or less in size between 1995 and 2002; of these 2547 underwent radical nephrectomy while 556 patients underwent partial nephrectomy. Their results concluded that radical nephrectomy was associated with significantly greater risk of both mortality and cardiovascular events.[12] In contrast, Larcher et al, on analysis of 1783 patients, found that radical nephrectomy was not associated with higher mortality from other

causes. Nevertheless their study findings suggested that patients with higher morbidities would benefit the most from partial nephrectomy.[13]

Scosyrev et al on behalf of EORTC compared renal dysfunction between patients who underwent radical or partial nephrectomy and could establish a difference in favor of partial nephrectomy for moderate renal dysfunction, but there was no difference in severe renal dysfunction and end stage renal disease(ESRD) between both treatment arms.[14] In the same context, Borregales et al found that partial nephrectomy was significantly associated with a lower incidence of development of end stage renal disease in patients with moderate renal impairment with estimated GFR 30-60 ml/min/1.73 $m^2$(calculated by the Cockcroft-Gault formula).[11]

## Laparoscopic Nephrectomy

Laparoscopic radical and partial nephrectomies have shown equivalent results in terms of oncological clearance as compared to open surgery. However, this can be technically demanding especially with partial nephrectomy. Becker et al compared laparoscopic radical, partial and open partial nephrectomies in 2277 patients and found that both laparoscopic and open partial nephrectomies had significantly higher surgical complications when compared to laparoscopic radical nephrectomy; more specifically: bleeding and genitourinary complications[15]. Dunn et al, as early as year 2000, compared open to laparoscopic radical nephrectomy and found that the latter had significantly more operative bleeding and costs, while patients in the same group required less analgesia and had shorter convalescence periods. However, recurrence rates and median survival was the same in both groups.[16]

A smaller non- randomized study by Hemal et al including 112 patients compared open to laparoscopic radical nephrectomy and found that bleeding was lower in the laparoscopy group along with shorter hospital stay and convalescence. Both groups had similar 5 years survival rates.[17] In the same context, Xu et al in a retrospective review of 843 patients found that open radical nephrectomy had significantly higher complications than laparoscopic radical nephrectomy, but there was no difference between the two procedures for partial nephrectomy.[18] Gill et al, prospectively and partly retrospectively evaluated 1800 patients who underwent partial nephrectomy open (1028)or laparoscopic ( 771) partial, and found that laparoscopic surgery had significantly shorter operative time; less blood loss; and shorter hospital stay. However, urological complications were higher for the same group but there were no differences between the two groups in renal functions at 3 months and 3 years or cancer-specific survival.[19]

Lane et al in a study comparing 10 year survival following open or laparoscopic partial nephrectomy found there was no difference in outcomes. In fact this was influenced by patient's age and presence of an absolute indication for partial nephrectomy.[20] Mac Lennan et al in a systematic review of 34 studies (6 RCTs and 28 NRSs) found that laparoscopic as compared to open nephrectomy had equivalent overall and cancer- specific survivals. However, overall survival was found to be better with partial nephrectomy which was equivalent between open and laparoscopic surgeries.[21]

## Robotic Surgery

Development in surgical technology, more specifically minimally invasive surgery, presents the attractive robotic and robotic- assisted laparoscopic partial nephrectomy as an alternative providing the advantages of shorter learning curves, easier dissection and suturing. Superselective clamping of renal vasculature instead of main artery is another benefit of robotic partial nephrectomy with no additional surgical complications.[22]

Lecomte et al compared 220 robot -assisted laparoscopic partial nephrectomies to 45 laparoscopic surgeries and concluded that the former provided for shorter operative time and overall hospital stay.[23]

Zhang et al performed a meta- analysis comparing laparoscopic to robot- assisted partial nephrectomy and found no differences between the two procedures in terms of operative time; hospital stay; estimated

blood loss; surgical complications; or state of surgical margins. However, their analysis showed that mean ischemia time favored robotic surgery, an element with well established role in future renal functions outcome.[24] Another systematic review comparing radical nephrectomy between robotic and laparoscopic surgery found higher costs and operative times in association with robotic radical nephrectomy. On the other hand, robotic surgery when compared to open radical nephrectomy , yielded lower operative blood losses; shorter hospital stay; and less need for postoperative analgesia.[25] However studies evaluating long-term oncological outcomes of robotic nephrectomy are yet to be published.

## Lymphadenectomy and Adrenalectomy

Perceived benefits of lymphadenectomy with radical nephrectomy include accurate staging; decreased local recurrence; and improved survival. This is thought to be of only limited value in locally-advanced tumors since blood born metastasis is usually present at the time of lymph node invasion. However, this has no role in localized renal tumors.

Ibrahim et al in a small retrospective study established a relationship between pathological grades of renal cell carcinoma and the presence of lymph node metastasis but overall survival was not influenced by presence of nodal metastasis according to their findings .[26] Similar findings were reported by Terrone et al who also added the relation between number of resected nodes and the presence of metastasis.[27]

In 2004 Blute et al retrospectively evaluated 1,652 patients and found multiple factors to be significantly associated with presence of lymph node involvement. These included: grade pT3 and pT4; tumors 10 cms or greater in size; sarcomatoid component presence; histological tumor necrosis; and nuclear grade 3 or 4. They suggested the use of these features to perform extended lymph node dissections.[28]

Whitson et al in a retrospective cohort of 9,586 patients established the relationship between the extent of lymphadenectomy and patients survival in those with lymph node metastasis.[29] However, the prospective EORTC renal cancer study group, when randomized localized renal tumor patients to node dissection or not, found no significant differences between the two groups in: operative morbidity; overall survival; cancer specific survival; or disease progression.[30]

Routine adrenalectomy is no longer performed as part of radical nephrectomy. However, this should be considered with radiological or intra-operative findings suggesting involvement of the ipsilateral adrenal gland. Nason et al in a cohort of 579 patients compared adrenal sparing to non adrenal sparing nephrectomy and found that 1.9% of patients had adrenal involvement, and concluded that adrenal sparing surgery patients had a significantly higher overall survival and cancer- specific survival (79.5% vs 63.3%) and (84.3% vs 74.9%) for the respective outcomes.[31]

Bekema et al, in a systemic review including 252 studies evaluated the outcomes of both adrenalectomy and lymph node dissection in locally-advanced renal cell carcinoma (T3, T4) and found that 5 year survival was improved with lymph node dissection but no oncologic benefits were found on addition of adrenalectomy to surgery.[32]

## Renal Cell Carcinoma with Inferior Vena Cava Thrombus and Metastatic RCC

RCC with inferior vena cava thrombus (10-25%) carries a poor prognosis with worsening prognosis with the level of proximal extent of thrombus ,with a propensity towards even worse prognosis with invasion to the venous wall (25% -5 years survival).

Multiple authors suggest aggressive surgery is the best treatment option (cytoreductive radical nephrectomy and venous thrombectomy )in patients who are otherwise fit for surgery as this improves 5 years survival up to 50%. The factors thought to influence prognosis include: distant metastasis (7% 5 years survival) and presence of venous wall invasion. Unexpectedly, the level of the thrombus does not influence prognosis. In fact,

it affects surgical morbidity in terms of the need for cardiopulmonary bypass in most proximal venous thrombi (supra-diaphragmatic). [33, 34]

Metastatic Renal cell carcinoma carries a poor prognosis. Recently, 3 retrospective studies evaluated the role of cytoreductive nephrectomy in patients treated with targeted therapy and results of these studies concluded that cytoreductive nephrectomy improved survival (20.5 months vs 9.5months), (19.8 vs 9.8 months) and (13.6 vs 7.8 months) in patients subjected to cytoreductive nephrectomy plus vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) -targetd therapy for the first 2 studies and alpha interferon 2b for the last study.[35-37]

Metastectomy has been shown to improve survival in patients with metastasis. Lin et al in a retrospective review of 295 patients with bone metastasis found that single and bone only metastasis had a better survival: the 30 days operative mortality was 5%. The reported survivals at 1 year and 5 years following surgery were 47% and 11%.[38] Similarly, Baier et al performed resections for pulmonary metastasis in 237 patients and reported 88% 5 years survival and found a significant association between survival and number of metastatic lesions and completeness of resection.[39]

## Recurrent Renal Cell carcinoma

Recurrence will occur after radical surgery in up to 40% of patients with RCC. Multiple factors are implicated including : incomplete resection; overlooked metastasis in ipsilateral adrenal gland or regional lymph nodes; and tumor implantation. Recurrence before or after 5 years from initial resection is the landmark to categorize early or late recurrences and correlates with prognosis which is worse in early recurrences.

Several retrospective studies comparing outcomes for resection of local recurrence and metastectomy have shown improved 5 years survival, particularly in those with single metastasis and prolonged disease- free intervals. Other factors favoring outcomes included: age younger than 60 years; lung metastasis as compared to brain metastasis. A few studies reported that outcomes were equal for the first and subsequent resections as well.[40, 41]

Itano et al, compared the outcome of surgery to systemic therapy or observation and achieved 5 years survival of 51% of patients with surgical resection of recurrence at renal bed compared to 18% and 13% after other treatment modalities.[42] Margulis et al, on evaluation of 54 patients with recurrent disease identified the size and positive surgical margin of recurrent mass; sarcomatoid features ; and raised serum alkaline phosphatase as adverse risk factors for outcome after recurrence. Their study also demonstrated survival benefit of surgical metastectomy.[43]

## Surveillance

Contemporary practice guidelines place patients on long follow- up surveillance protocols owing to the high recurrence rates and some recurrences occurring even long after curative surgery (more than 10 years- (45 years in one case report). Additionally, early intervention in few metastatic (less than 5) and recurrent disease provides the best outcomes so far.

Recurrence rate for pT1 tumors is in the range of 7% with recurrence occurring in the lungs at median follow up of 35-37 months. pT2 tumors recur in up to 27% at a median of 25-32 months. pT3 tumors recurrence is reported around 39% with a median of 14-9 months for T3a and b tumors. Lymph node positive tumors will recur in 70% of patients with a median recurrence of 9 months.[44]

The University of California at Los Angeles (UCLA) placed a protocol for follow- up based on their risk group stratification system. Patients at low risk of recurrence should have: annual history and examination, laboratory tests, chest CT and abdominal CT at 2 and 4 years and no follow- up beyond 5 years. Intermediate risk patients are to receive: history, examination, laboratory tests and CT chest every 6 months for the first 3 years then annually for 10 years with an abdominal CT at 1 year then every 2 years. High risk patients should

receive the same follow up as intermediate risk patients with abdominal CT every 6 months for first 2 years then annually up to 5 years, then every 2 years for 10 years.[45]

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# Review

## The Role of non-surgical options in the treatment of renal cancer:

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### Introduction:

Renal cancer accounts for almost 2--3% of all cancers in adults, male female ratio is 3:2, and in 4% of the cases the disease is bilateral. (1, 2). Adencarcinomas form 80 - 90% of all primary renal cancers, which arise from the renal cortex. The second cancer is transitional cell cancer arising from the renal pelvis. Other rare renal cancers include: oncocytomas, sarcomas and medullary cancers. It's more prevalent in the 6 – 8th decades of age, (3, and 4)

Despite improvement in diagnosis, 20 –30% of patients present with metastatic disease and another 20 % of patients undergoing nephrectomy will later develop metastases. The etiology of RCC is unknown but obesity and smoking are risk factors .The highest incidence was reported from Europe, North America and Australia, while rates are low in Africa, India and Japan. In Sudan it forms about 1.5 % of all cancers in adults. (3, 4).

### Pathology

The 2004 WHO classification of renal cancers is:

Clear cell cancer (70%); papillary cancers (10 -15%); chromophope tumors (15 %). Other rare renal cancers include: cancer of the collected ducts of Billini; renal medullary cancer; XP12 translocational cancer; multi-locullar clear cell cancer associated with neuroblastoma; mucinous tubular and spindle cell cancer; and unclassified renal cell cancers. Sarcomatoid and rhabdoid differentiation are rare findings that may occur in any subtype with highly aggressive behavior. (5, 6, 7).

### Staging

There are many staging systems used, but Robson modification of Flocks and Kadesky is not complicated and is commonly used in clinical practice.

Stage one: tumor confined within the capsule.

Stage two: tumor invading the perinephric fat but still contained within the gertora fascia.

Stage three: tumor invading the renal vein or the inferior vena cava = A, or involving regional nodes = B, or both = C, (8, 9).

### Surgery

Surgery remains the main and the most effective treatment for nlocalized disease .It's also used for treatment of metastases and local recurrence as a palliative treatment. Most urologists perform open nephrectomy, with either a retroperitoneal or transperitoneal approach. In the 1960th Robson described the operative principles of radical nephrectomy, which became the gold standard treatment for localized renal cancer. (10, 11).

### Radiotherapy

Preoperative radiotherapy and postoperative radiotherapy failed to show any advantage in disease free survival (DFS), or overall survival (OS), based on 2 preoperative and 2 postoperative radiotherapy negative trials. (12, 13)

Radiotherapy can be used in the treatment of unresectable disease, recurrent disease and metastatic disease as a palliative treatment, to improve local control and relieve symptoms. (13)

## Prognosis

Despite recent advances in the treatment of renal cell cancer, the prognosis remains poor, with an estimated 5 years survival of 11 %.[1] The disease is resistant to chemotherapy, and a small subset of patients respond to immunotherapy[2,3]. The introduction of the Tyrosine Kinase Inhibitors, Sunitinib , Pazopanib and Axitinib , and the Vascular Endothelial Growth Factor( VEGF); directed Monoclonal Antibody Bevacizumab ,used in combination with interferon and the Mtor inhibitor ( Everolimus ), and Temsolinimus , increased the progression- free survival (PFS), compared with immunotherapy and placebo. [14]

Many prognostic factors influence treatment decisions and outcome e.g. the pathology is a key factor. Most of the available data are in patients with clear cell renal ca, which accounts for 70 –80 %of the cases. Papillary renal cell cancer, 10 –15%, with a similar prognosis to clear cell RCC; and chromophope renal cell cancer which forms about 5% of the cases has a better prognosis, [15, 16]

Other prognostic factors e.g the Memorial Sloan Kettering model which stratified prognosis as favorable , intermediate or poor based on serum lactic dehydrogenase ( LDH), performance status ;serum calcium level >10mg /dl, Hg level less than the lower level of normal; and time from diagnosis to treatment . Score zero has a favorable prognosis ;1-2 factors is intermediate risk; 3 -5 is poor prognosis ,which are associated with: 30,14,5 months median survival respectively. The model was developed for patients treated with interferon-based regimens to identify patients who may benefit from immunotherapy. [17, 18]

## Immunotherapy

Alpha interferon daily subcutaneous dose of 5 – 10 million units produces an objective response of 13-15%.The common side effects are flu-like ,fever, chills, anorexia ,muscle ache ,headache and fatigue .The response is usually slow . In a large study of 246 patients randomized to nephrectomy and alpha interferon vs nephrectomy alone ,showed a median survival of 11.1 vs 8.1 months in favor of the alpha interferon group (p = 0.05) and overall survival of 17 vs 7 months in favor of alpha interferon group( p= 003) .[19,20] Alpha interferon and interleukin 2,IL2, were the first approved agents for metastatic RCC, and for two decades this was the standard care. Interferon improves overall survival by 2.5 months compared with hormonal treatment with medroxy progesterone acetate . Its use is limited by adverse effects e.g. influenza like symptoms ,and fatigue ,but these are usually grade 1 or 2.[20]

High dose IL2 produces complete response in 5 – 7% of patients in patients with advanced RCC .It should be considered in patients with excellent cardiopulmonary reserve. Its use is associated with 14% incidence of treatment -related deaths and fever,chills, fatigue ,hypotension , nausea and vomiting [21,22]. Both agents can produce durable responses that can last for years. From the analysis of 7 phase 2 trials, of 255 patients, treated with high dose IL2, complete response was achieved in 7% of patients and partial response in 8 %of patients. Median duration of CR was 80 months and 20 months for PR patients. There is no known factors that can identify patients who will benefit from immunotherapy. [22, 23]

### Targeted treatment first line

Sunitinib is an oral multikinase inhibitor. A dose of 50 mg daily for 4 weeks and 2 weeks off in favorable and intermediate risk group patients ,resulted in PFS of 8 – 9 months. There are some safety concerns with regard to fatigue,hand foot syndrome ,diarrhea and hepatic toxicity. So Sunitinib is used as a first line for all prognostic groups patients, particularly those with aggressive disease who are younger and fitter,and less appropriate for elderly patients with co- morbidities. [24]. In a phase 3 study of 750 new patients with clear cell RCC, comparing sunitinib vs alpha interferon ,the median overall survival was 11 vs 5 months in favor of sunitinib. Overall survival showed a statistically non- significant trend in favor of sunitinib : 26.4 vs 21.8 months (p= 0.051).[24,25]

## Pazobanib

Is a multikinase inhibitor . It was investigated in a phase 2 study, as first line treatment in 233 patients ,dose 800 mg daily. The median survival was prolonged by 9.2 months vs. 4.2, (p value <0.0001). 53% of these patients developed elevation of transaminases ,in addition to fatigue and anorexia in 19 – 22 % respectively . Currently pazopanib seems to be a reasonable alternative option to sunitinib in patients with good and intermediate prognosis. [26] It was evaluated in a placebo- controlled international study of 435 patients with clear cell RCC ,50%of them had cytokine therapy, and 50% were naïve .The progression- free survival ,PFS, in the pazbanib group was 9.2 vs 4.2 months in the placebo group (p= 0.0001).[27]

## Bevacizumab and alpha interferon

Bevacizumab was approved by the FDA in 2009 for the treatment of metastatic RCC .The reported median PFS of bevacizumab and interferron ranges between 8.5 –16.8 months in the AVOREN,CALGB, and the TORAVA Studies .Patients with favorable and or indolent disease may be particularly suitable for bevacizumab and interferon therapy.[28,29,30] Bevacizumab and alpha interferon as a first line treatment resulted in a longer PFS ,but not overall survival compared with alpha interferon alone.[30]

## Sorafenib

Many phase 2 studies of first line sorafenib ,showed a median PFS of 5.7 – 9 months. In phase 3 trials sorafenib was associated with lower rates of diarrhea (48 vs. 61), nausea(19vs 52 %) , fatigue( 29 vs. 54 %),vomiting (12 vs. 31 %) and hypertension (17 vs. 30%), compared with sunitinib ,but similar rates of hand foot syndrome (33 vs. 29%.[300]

Sequential targeted therapies should be considered in all patients able to tolerate them, particularly those with minimal co- morbidities and younger patients. Several retrospective studies have shown benefit of a sequence of sorafenib and sunitinieb. [31, 32]

## Temsirolimus

Is an intravenously given mTOR inhibitor . It was approved by the FDA in May 2007,and in the *NCCN kidney cancer panel recommendations as a category A* for first line treatment for patients with poor prognosis ,relapsed or unresectable or metastatic RCC. In a study of 626 patients randomized for temsirolimus 25 mg/week, vs. alfa interferon alone vs. temsirolimus 15mg and alfa interferon, patients treated with temsirolimus had a longer overall survival (OS), than those treated with alfa interferon alone, (10.9 vs. 7.3 months) median survival (p value = 0.003). Adverse events include: rash, stomatitis, pain, infection, peripheral oedema, thrombocytopenia, neuropathy, hyperlipedemia, hypercholestremia and hyperglycemia.[33, 34, 35]

## Everolimus

This is an oral m Tor inhibitor. It was approved by the FDA in 2009, as a second line treatment after sorafenib or sunitinib failure. In a phase 3 study in patients failing sunitinib and or sorafenib in 410 patients, randomized into everolimus 10mg daily( 272 patients ) vs. placebo (138 patients), everolimus produced significantly better PFS, 4 months vs. 1.9 (p value = 0.0001). Its side effects included: stomatitis 40%, rash 25 %, fatigue 20%, non- infectious pneumonitis 3 %.[36]

A large randomized phase 2 study ( RECORD Study), showed that the standard sequence of multiagent tyrosine kinase inhibitors: sunitinib followed by everolimus, extended survival compared with the reverse. [37]

## Chemotherapy

RCC is refractory to most chemotherapy agents, because of multi-resistance mediated by p glycoprotein. A phase 2 trials of gemcitabine 600 mg /$m^2$, day 1, 8 and 15, and 5 FU, 150 mg/$m^2$ continuous daily infusion for 21 days, in patients with metastatic RCC, produced a partial response in about 17% of patients without any complete response.[38]

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# Glutamic acid decarboxylase autoantibodies in Sudanese diabetic children and their siblings

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## Abstract

**Background:** Type -1 diabetes mellitus(T1DM)is known to be an autoimmune disease . Glutamic acid decarboxylase (GAD) is the enzyme responsible for the conversion of glutamic acid into the inhibitory neurotransmitter gamma amino butyric acid (GABA).GAD is a major auto antigen in type 1 diabetes ,being recognized by auto antibodies present in sera of the majority of patients at onset of the disease . It is also one of the important predictive immunological markers in developing the disease among first degree relatives.

**Objectives:** (a) To determine the prevalence of anti- GAD antibodies in Sudanese diabetic children , their healthy younger siblings and the control group. (b) To evaluate the presence of GAD antibodiesas an indicator of autoimmunity in T1DM in Sudanese diabetic Children .

**Methods:** This is a hospital- based, prospective, case- controlled study.The patients were randomly selected from diabetic children attending two hospitals in Khartoum State **.**Sixty –five diabetic children , 25 of their healthy siblings and 31 healthy controls were enrolled . A precoded questionnaire was completed . The presence of GAD antibodies was investigated for the study subjects,their siblings and control subjects using Diamyd Anti GAD65 Radioimmunoassay.

**Results:** The majority of diabetic patients were between 11 – 15 years representing 37(57.1%). Antibodies to glutamic acid decarboxylase { considered by the lab to be positive if >10.2 U/ml } .GAD antibodies were found to be significantly positive in 30 (46.1%) of the diabetic children compared to only one (3.2 %) of the controls , P- value was highly significant { $P < 0.0001$ } . Highest titers were detected in diabetics with disease duration over one year . GAD antibodies were tested in 25 of siblings.Significant titers were detected in only 2 of them representing 8% .

**Conclusions:** It was concluded that GAD antibodies is an important immunological marker in Sudanese children with IDDM and similar to Asian and European populations , However, further research using other tests like antibodies against insulin(IAA) , islet cells (ICA) and zink transporter 8 (ZnT8Ab) as well as insulinoma- associated -2 autoantibodies (IA-2A) would be more specific .The role of GAD in disease prediction among siblings needs further research

## Introduction

Diabetes mellitus is a common chronic metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are classified according to those caused by deficiency of insulin secretion due to pancreatic beta cell damage (T1DM) and those that are a consequence of insulin resistance.(1) Type 1 diabetes mellitus, the commonest endocrinological disorder occurring in childhood ,is the end point of many disease processes resulting in progressive loss of beta cell function and insulin deficiency .

The disease is quite distinct by its association with certain histocompatibility antigens (HLA) ;the association with circulating antibodies for cytoplasmic and cell surface components of islet cells; antibodies for insulin and glutamic acid decaroxylase (GAD) antibodies.

GAD is highly expressed in the central nervous system. It is also found at lower concentrations in several other tissues.But ,after the CNS ,the Islets of Langerhans, are the tissues where highest GAD activity is expressed.[2]

In patients positive for anti- GAD antibodies, there was a strong association with other organ-specific autoimmune diseases, such as insulin-dependent DM, hypothyroidism, Grave's disease and pernicious anemia.[3]

Antibodies against the 65-kDa isoform of glutamic acid decarboxylase ($GAD^{5,6}$) can be applied as a predictive tool for childhood type-1 diabetes and to facilitate the differential diagnosis of diabetes in adults.[4]

Anti-GAD antibodies has recently been recognized as a reliable immunological marker for type 1 diabetes.[5,6] Recently, researchers became more interested to evaluate risks of autoimmunity.[5] In UK one study was concerned with determinants of risk in HLA DR3 –DQ2/ DR4 –DQ8 siblings .GAD auto antibodies affinity is being tested to identify specific epitopes profiles in children at risk for T1DM.[7,8] In the Diabetes Prevention Trial-Type 1 Diabetes (DPT-1), subjects at high risk for developing diabetes were followed with serial IVGTTs and oral glucose tolerance tests (OGTTs), and in a subsequent study, the metabolic factors associated with progression to diabetes were evaluated.[9] In another study, an autoantibody response directed to the extracellular domain of IA-2 was associated with very high risk of type 1 diabetes progression, suggesting the presence of new antigenic determinants within the extracellular domain of IA-2 .[10] Type 1 diabetes is closely related to both cellular and humoral immune responses to insulin producing beta cells. Antibodies to glutamic acid decarboxylase(GADA) and islet cell antibodies (ICA) have been observed to persist after the diagnosis of diabetes mellitus and with highly fluctuating concentrations for GADA.[11 ,12]

## Patients and Methods

This prospective, cross-sectional, case-controlled, hospital-based study was conducted in Khartoum State during the period from Aug1998 - Aug1999.

The study population consisted of 3 groups:

**Group A:** 65 diabetic children aged 1-1 6 years attending two diabetic centers in Omdurman and Khartoum . Sample size was calculated according to the formula:

**Group B:** 25 healthy younger siblings of group A.

**Group C:** 31 healthy children matched with group A for age and sex with no family history of type 1 diabetes, thyroid disease or autoimmune diseases and were selected from surgery and orthopedic referred clinics in Omdurman Hospital .

An informed consent was taken from patients , controls and parents or care takers.

Group A patients were individually interviewed by the author. The research objectives were fully explained; a pre-coded questionnaire including: socio-demographic characteristics, clinical features and insulin requirements was completed .

Evidence of autoimmune diseases and complications of diabetes mellitus were also noted .

The other groups (B&C) were interviewed and an informed verbal consent was obtained. Finger prick blood testing was done using Glucometer (Sensor ,Boeringer M). Urine was tested for glucose , ketones and albumin using dipsticks .

5 ml of venous blood was taken from all 3 groups using vacutainer needles : 2 mls were put in the EDTA container , 3mls were separated and serum was put in 2ml containers .Samples were kept frozen till being sent abroad for testing .

Group B were interviewed by the author and 3 mls of venous blood were taken using vacutainer needles. Two mls were put in the EDTA container

and the rest was centrifuged

The sera of all the 3 groups were stored in _20 degrees C to be shipped in dry ice to the laboratories of the Dept. of Internal Medicine & Endocrinology – Uppsala University – Sweden .

Anti-GAD antibodies were measured in the sera of the 3 groups using Diamyd antiGAD 65 Radioimmunoassay, which is a solid phase direct radioligand assay ( manufactured by Diamyd Diagnostics AB Stockholm, Sweden ) .During incubation antiGAD antibodies in the samples and I -125 labeled GAD 65 formed a complex.Then, the formed antigen- antibody complex was separated by centrifugation.Then, the centrifugation was measured by measurement of radioactivity which was directly proportional to the anti-GAD titer in the sample .

Data were entered in the computer using Epinfo version 6 .Simple tabulation was done .Chi Square test was used to the 95% significance level. Linear regression analysis was also used to determine the relation and to calculate the correlation coefficient (r) between GAD antibodies and various parameters

The task of patients selection, interviewing,questionnaire completion and blood sampling were all conducted by the author.

## Ethical Considerations

Medical problems of diabetic children were dealt with either by the author herself, or else, by referral to hospital.

The study was approved by The Ethical and Research Committee, Faculty of Medicine, University of Khartoum as well as relevant authorities in Uppsala University, Sweden . Permission from the health authorities and consultants in Omdurman and Khartoum hospitals was obtained

## Funds & Grants

The study was self-funded and partially funded by the Department of Internal Medicine, Uppsala University, Sweden who performed the laboratory work .

## Results

We studied 65 diabetic children , 25 siblings and 31 healthy children as controls. Ages of diabetics varied from 1.5 -16 years .The mean (+or – S.D.) age was 8.75 (3.4)years, compared to an age range of 1.5 -15 ,the mean (+or-S.D.) .The predominant age group among diabetic children was 11 – 15years representing 37(57.1%) (**Table 1)**. Males predominated in both groups. M/F ratio was 1.3 : 1 and 1.27 :1for diabetics and controls respectively.

Twenty nine (44.6%) of the diabetics were from Gaaliyeen Tribe. Poverty and Illiteracy predominated in parents of diabetics and controls .

Newly discovered diabetics were 23 (35.3%). The same number existed for duration of 13 – 36 month. Eleven patients (17%) had a disease for 37-60 month. Only 8 patients (12%) had the disease for more than 5 years **.**

Antibodies to glutamic acid decarboxylase ( considered by the lab to be positive if >10.2 U/ml) were detected in significant levels in the sera of 30 (46.1%) of the diabetics compared to only one (3.2 %) of the controls ,P- value was highly significant($P < 0.0001$) .

GAD positive patients with levels of 8-20% were 8 (12.3%) compared to one (3.2%) of the controls .Levels of 21 -60% of GAD were found in 14(21.5%) of the diabetic children **(Table 2)**.

Very high levels of more than 60% were detected in sera of 8 (12.3%), the only child from healthy controls who was GAD positive had a level of 21 U/ml ,considered as moderately high .

Nine patients (39.1%) of the newly discovered (duration < than 12 month) were found to be GAD positive .

## GAD in the Siblings of diabetic children

Twenty five healthy siblings of the diabetic children were included in the study , majority of them were in the age group of 6-10 years and comprising 10 (40.0%) . Eleven (44%) of the siblings aged more than 10 years **(Table 3)**.

GAD antibodies were tested in 25 of the siblings. Significant titers were detected in only 2 of siblings representing 8% while it was detected in one (3.2 %) of the study group.

The first sibling had moderately elevated levels. She was a female of 15 years with no abnormality on clinical examination. The second one was a sibling of 2 diabetics.He was 12 year boy with significantly high levels(> 450) U /ml **(Table4)**.

**Table 1.Age distribution of the diabetic children (Group A, n = 65) and the controls (Group C, n = 31**)

| Age (years | Diabetics n (%) | Control n (%) |
|---|---|---|
| 1.5 – 2 | 2(3.1%) | 1(3.2%) |
| 3 – 5 | 8(12.3 %) | 3(9.6 %) |
| 6 – 10 | 10(15.3 %) | 8(25 .8%) |
| 11 – 15 | 37(57 %) | 19(61.4 %) |
| 16 | 8(12.3 %) | 0 (0.0%) |

P value = 0. 58

**Table 2.Antibiodies to glutamic acid decarboxylase "GAD" in the diabetic children (Group A, n = 65) and the controls (Group C, n = 31)**

| GAD Ab U/mL | GAD Ab % | Diabetics n = (%) | Control n (%) |
|---|---|---|---|
| 0 | 0 | 26(40.0) | 28(90.3) |
| < 10.2 | < 7 | 9(13.9) | 2(6.5) |
| 10.45 – 28.85 | 8-20 | 8(12.3) | 1(3.2) |
| • 29.55 – 450 | 21-60 | 14(21.5) | 0(0.0%) |
| • 450 | > 60 | 8(12.3) | 0(0.0) |

GAD levels are expressed in units per ml with the corresponding percentage from the nomogram

(df = 1, $X^2$ = 15.78, p < 0.0001)

**Table 3. Age distribution of the siblings of diabetic children (Group A, n = 25) and the controls (Group C, n = 31)**

| Age (years) | Siblings n (%) | Control n (%) |
|---|---|---|
| < 1.5 | 1 (4.0%) | 0 (0.0%) |
| 1.5 – 2 | 2 (8.0%) | 1 (3.2%) |
| 3-5 | 1 (4.0%) | 3 (9.6%) |
| 6-10 | 10 (40.0%) | 8 (25.8%) |
| > 10 | 11 (44.0%) | 19 (61.4%) |
| **Total** | **25 (100%)** | **31 (100%)** |

P value = 0.24

**Table 4. GAD antibodies among siblings of the diabetic children (Group A, n = 25) and the controls (Group C, n = 31)**

| GAD Ab U/mL | GAD Ab % | Diabetics n = (%) | Control n (%) |
|---|---|---|---|
| 0 | 0 | 23 (92.0) | 28 (90.3) |
| < 10.2 | < 7 | 0 (0.0) | 2 (6.5) |
| 10.45 – 28.85 | 8-20 | 1 (4.0) | 1 (3.2) |
| • 29.55 – 450 | 21-60 | 0 (0.0) | 0 (0.0%) |
| • 450 | > 60 | 1 (4.0) | 0 (0.0) |
| Total | | 25 (100.0) | 31 (100.0) |

- GAD levels are expressed in units per ml with the corresponding percentage from the nomogram. (Fisher exact test: P = 0.58)

## Discussion

The presence of GAD auto-antibodies was detected in significant levels in the sera of nearly half of the diabetics compared to only one (3.2 %) of the controls ,P- value was highly significant( P < 0.0001). This frequency was higher than that reported in the European study where less than tenth of the patients were found to have significant titers for GADA[12] ;but the comparison could be rather difficult if we consider that in the latter, patients with longer disease duration were tested for presence of GADA. However, it wasn't the same

in a study among Spanish population of T1DM children where two third of them tested positive for GADA[13] .

Our findings were rather similar to reports from South Africa and Ethiopia reporting higher rates of auto antibodies in patients T1DM [14,15] , while it was not the same in Tanzania and Nigeria [16,17] , where lower levels of less than tenth of the patients had positive auto antibodies. On the other hand, in line with our study, significantly positive titers were detected in nearly half of the study population of Tunisian children.[18]

Compared to Asian populations, our results were higher than that obtained in the Chinese study which reported one quarter as positive for GADA [19]; while nearly half of the T1DM patients in the Saudi study were found to be positive for GADA[20]

These differences from European and Asian populations could be related to ethnic variations or probably to the rare DR4/ DQW2 haplotype previously reported by Almagzoub.[21 ]

In this study, children with longer disease duration had increased frequency of positive titers than those with disease duration less than one year. That is contradictory to the results of European and Saudi researchers who described younger patients with shorter disease duration.[12,20]

The same was obtained by Yokota et al.[22] On the other hand, titers were found to be lower in children with longer disease duration among Tunisian children.[18]

In agreement with the literature, no relationship of GADA with age and gender was found.[23] However, female predominance had been observed in European as well as Saudi patients.[12,20]

GADA was only found in 2 siblings of patients compared to one of the controls. Higher frequency was found among first degree relatives of Spanish population of patients with T1DM.[24] It is also lower than the incidence reported among 882 American first degree relatives of Type 1 diabetics where 90 % proved to be serologically positive and later developed T1DM.[25] Our findings may be explained by the small sample size of the siblings enrolled and lack of follow- up in our study.

Predictive characteristics of GAD auto-antibodies also depends on genetic markers. A study in Finland in an unselected population of 701 siblings of children with type 1 diabetes siblings carrying the protective DR2 and DQB1 *0602 -3 alleles were characterized by lower frequencies of ICA , IA and GADA.[26]

Risk of diabetes associated with HLA DR3-DQ2-DQ8 in U.K families was studied among 2,134 siblings and followed to a median duration of 22 years. In HLA identical DR3 –DQ2 / DR4 /DQ8 siblings, the cumulative risk of diabetes by age 15 was 17% versus 6% in those sharing one haplotype or none( P= 0.095) [27,28]. Relatively similar to our results, frequencies of GAD antibodies were detected in sera of siblings of Syrian and Jordanian diabetic children , 1(1.3%) and 2(2%) respectively. Those are considered among the highest reported in the world. This would ,more than ever, highlight the evidence of occurrence of a true autoimmune type of diabetes in Sudanese children.[29]

## Recommendations

The study emphasizes the importance of GAD auto-antibodies as an immunological marker in children with T1DM and could add to the value of antibodies in disease monitoring and its complications . Because prevention of type 1 diabetes is still at the stage of research trials, the trials are often mentioned in the popular press. As a result, many patients with type 1 diabetes (or their parents) ask their doctors about screening of other family members (particularly children) and what could be done if the family member has a high risk for the development of type 1 diabetes?. The role of GADA in disease prediction among siblings of diabetic children needs to do further research using larger samples, additional predictive antibodies, genetic markers and follow- up.[29,30]

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# Marjolin's ulcer at Soba University Hospital, Khrtoum, Sudan: a case series of fifty patients

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**Background:** Marjolin's ulcer (MU) is a rare aggressive skin malignancy that complicates chronic non-healing wounds and scars. Studies have been conducted worldwide to report the risk factors and clinic-pathological features of this disease. Sudanese literature on the subject is scarce.

**Objective:** To describe the clinico-pathological features of Marjolin's ulcer (MU) among a sample of Sudanese patients who have been diagnosed with MU at Soba University Hospital (SUH), Khartoum, Sudan.

**Patients and Methods:** This is a descriptive, analytical, hospital-based study. Data was collected from records of all patients with Marjolin's ulcer who were treated in the Unit of Plastic Surgery between 2008 and 2015.

**Results:** A total number of fifty patients were studied; male to female ratio was 2.8**:**1. The mean age was 43±12 years and the mean latency period (the mean period between scarring and the diagnosis of Marjolin's) was 10.3±5.7 years. Significant association was found between age and latency period ($P$<0.001). Forty two percent of patients had duration of illness for 1-5 years before presenting to hospital. Non-healing ulcers and increasing pain were the main presenting complaints (52% and 26% respectively). Burn scars were the most frequently reported risk factor (72%). Lower extremities were the commonest site (74%). The average tumor size was 9±2.5cm and the majority of patients (75.7%) had tumor size of ≥5 cm in diameter. In addition, regional lymph nodes were clinically palpable in 15(30%) patients, while 11 (22%) patients had distant metastasis at the time of presentation. Squamous cell carcinoma (84%) was the most reported histological variant and surgery in the form of wide excision of the ulcer and split-thickness skin graft or flap coverage was performed in 41(82%) patients.

**Conclusion:** Clinico-pathological features and risk factors of Marjolin's ulcers in our case series are similar to regional reports with characteristic shorter latency period and advanced clinical stages at the time of presentation. Biopsy of chronic non-healing ulcers is needed to exclude Marjolin's ulcer and to allow early diagnosis of the disease.

## Introduction

Marjolin's ulcer (MU) is a rare and aggressive malignant condition that arises on chronic skin lesions and represents about 1.2% of all skin cancers.[1-3] The precise mechanism by which chronic skin lesions develop malignancy is not well understood and many theories have been postulated.[4,5] Nevertheless, it is possible that multiple mechanisms may play a role in malignant transformation of chronic skin lesions.[5] Chronic irritation and repeated traumas induce cell mitotic activity of regeneration and repair leading to malignant changes.[6, 7]

Burn scars are the most frequently reported initial skin insult.[1-6] However, other risk factors were also reported including: chronic infections, bed

ulcers, chronically traumatized skin, animal bites and chronic venous ulcers [1-5]. The classic triad of nodule formation, induration, and ulceration at the scar site suggest the malignant transformation.[5, 6]

The lower extremities are most commonly affected anatomical sites.[1-7] Macroscopically, Marjolin's ulcers exist in two forms which are of prognostic importance: the *exophytic form* and the *infiltrative form.*[4] Squamous cell carcinoma is the most common histological variant resulting from malignant transformation, although other rare variants are reported in several studies.[5-7]

The management of Marjolin's ulcers requires multidisciplinary approach.[1] Surgery remains the main stay of treatment for MU. Wide local excision (WLE) with safe margins of 2 to 4 cm has been suggested by several authors and then reconstruction with skin graft or flap as decided by the site of the lesion.[5-8]

The current study aimed to report risk factors, latency period, clinical, histopathological features and management options of Marjolin's in patients who presented to SUH during the period from January 2012 to May 2015. To the best of our knowledge there are no similar reports on Sudanese patients.

## Patients and methods

This is a retrospective, descriptive, analytical, hospital-based study. Data were collected by reviewing medical records of patients who presented with Marjolin's ulcer to the plastic and reconstructive surgery unit.

A predesigned questionnaire was used to collect demographic and clinical data which included: patient's age, gender, original cause of skin lesion and its duration, site and size of lesions, regional lymphadenopathy and evidence of metastasis. Pathological diagnosis was established histologically in all patients and methods used in the treatment were also documented.

Data were analyzed using the SPSS software package (version 21 windows). To determine the statistical significance of differences the Pearson test was used and probability test (*P*. value) with $P < 0.05$ was considered as significant at 95% confidence interval.

## Results

Fifty patients were studied; males were 37 (74%) and females were 13 (26%) with male to female ratio of 2.8**:**1.

The mean age of the patients at the time of presentation was 43 ±12 years, the range was 19 to 67 years and 20 patients (40 %) were between 40-60 years of age. The duration of the ulcer in 42% of patients was 1-5 years before presentation and nearly one third (33.4%) of the patients presented five years after ulceration. The average latency period was 10.3 **±5.6 years and it ranged from 4 to 24 years , while it was significantly less than 10 years in those who were less than 40 years old(83%)***(P*<0.001).

Non-healing ulcers and increasing pain were the commonest presenting complaints in 52% and 26% of patients respectively.

Burn scars were the most common reported original insult factors (74%) followed by trauma and road traffic accidents in four patients (10.8%) **(Fig.1).** the lower extremities were the most affected location 38(76%) followed by head and scalp in eight (16%) cases.

The average size of the ulcers/ tumors was 9 ± 2.5 cm with a range of 4 to 22cm and in more than 77% of the patients the ulcer was 5 cm in diameter.

Regional lymph nodes were clinically palpable in fifteen patients (30%) and eleven patients (22%) had liver and or lung metastatic disease.

Incisional biopsy was performed in ulcers that exceeded 2cm in diameter (77%) and all patients with metastatic disease (22%), while in the rest excision biopsy was performed.

Treatments given before presentation to SUH included: topical antibiotics in 27%, of cases, herbal medicines by traditional healers in 32.3%,

topical antibiotics in 22% and 16% were on regular dressings at health centers, rural or peripheral hospitals. However, biopsy was advised before presentation in seven cases. Sixty percent of the patients were treated by wide excision and split-thickness skin graft.Wide excision and flap coverage was performed in 12%, and amputation in 10% of patients.

Lymphatic nodes dissection was performed in 13 patients (26%) **(Fig.2)** and the histopathology of all of them was positive for metastatic disease and 18% patients were re-treated by radiotherapy due to either small resection margin or incompletely excised tumor.

The histopathology results revealed: squamous cell carcinoma in the majority of cases (84%). Other histological variants were: basal cell carcinoma (8%), dermatofibrosarcoma (2%), leiomayosarcoma (2%). Pathological reports were not available in two (4%) of the patients.

**Table 1. Initial skin insult**

| Initial Skin Insult | Percentage (%) |
|---|---|
| Burn scar | 74 |
| Trauma | 11 |
| Chronic wounds | 5 |
| Pressure ulcers | 4 |
| Venous ulcers | 2 |
| Missing data | 4 |
| Total | 100 |

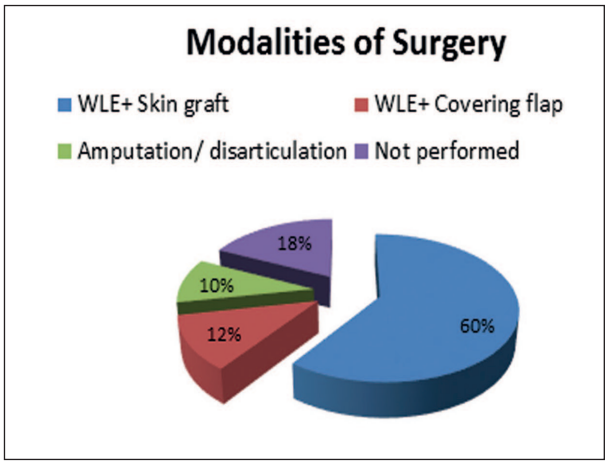


**Figure 1.Surgical modalities performed.**

## Discussion

The mean age of presentation in this series was 39.5 years which is quite similar to that found in regional reports from Tanzania (38 years) [1] and Nigeria (39 years) [9], but lower than that reported in Kenya (48 years) [10]. However, this mean age is far below that reported in USA (59 years) [11] and Iran (50 years) [12]. In fact, a number of confounding variables such as etiologic factors may influence this age of onset [3, 13]. Some regional literature has reported characteristic trends in the epidemiology of Marjolin's ulcers that affect young patients in particular.[14, 15]

In this report, a significant association was found between age at presentation and latency period i.e. younger patients had shorter latency period whereas 83.3% of those who were younger than 40 years had latency period of less than 10 years ($P$<0.001) , a finding which is in keeping with previous reports .[1, 5]

The average latency period was 10.3 years which is nearly similar to a reports from Tanzania (11 years) [1] , and it is lower than other African figures[10,16] , Nigeria (18 years)[16] and Kenya (19 years).[10] However, Nthumba reported a latency period of 16 years in African Sub-saharan patients [10]. The reasons for this relatively shorter latency period amongst African patients are not fully understood [1].

Sex distribution is fairly comparable to other reports i.e. a remarkably higher prevalence among

males [1-5], Environmental factors might explain this finding as males in general are more exposed to the risk factors. Nevertheless, sex- related genetic differences may also contribute to this observation[3]

In agreement with regional and international literature [1, 3, 4]; the burn scar was the most frequent cause of original skin insults (70%). In Sudan, Marjolin's ulcers were reported in 2.6% of burns patients who had conservative management which is similar to international literature.[17]

In keeping with the literature[1-7], the lower extremities were the most frequent sites of MU. This could be due to their vulnerability to trauma.

The advanced clinical presentation in our series (regional lymph nodes involvement and distant metastasis) is largely consistent with the pattern observed in other African countries [1, 2, 19]. However, late presentation is rare where health facilities are more available. [13, 18]

In Sudan, like other African countries, MU patients often present with advanced stages of the disease as a result of various factors including poor health, low awareness about chronic non-healing ulcers and lack of adequately trained staff and specialized centers. [19]

Similar to regional and international literature, squamaous cell carcinoma is the commonest histological variant (78.4%), followed by basal cell carcinoma (10.8%) and other rare variants have been also reported in this series.[1-6]

Surgery is the main stay of management of Marjolin's ulcers.[1-3] As in other reported series, wide excision and split-skin grafting was performed in 62.1% of patients.[1, 3, 5] Lymphatic node dissection was performed in 29.7% which is consistent with advanced clinical stages in our patients [3]. Prophylactic lymph node dissection was not performed as most authors agree that it is not usually recommended in the absence of clinical or radiological nodal involvement.[5]

Six patients (12%) were not offered surgery as they presented with metastatic disease and they received palliative radiotherapy. However, the literature reported poor response to radiotherapy as a result of poor vascularity of ulcers due to extensive fibrosis[20]

## Conclusion

Clinico-pathological features and risk factors of Marjolin's ulcers in the present series are comparable to what has been reported in regional literature. Younger patients presented after shorter latency period with advanced clinical stages. Biopsy of chronic non-healing ulcers is recommended to exclude Marjolin's ulcer and to allow diagnosis at an earlier stages.

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# Hemodialysis catheter-related complications in Khartoum Teaching Hospital Dialysis Centre.

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## Abstract

**Background:** The use of hemodialysis catheters maybe associated with mechanical and/or infectious complications. The rate of these complications is variable. In this study we looked at the hemodialysis catheter- related complications in Khartoum Teaching Hospital Dialysis Center.

**Methods:** This was a hospital-based, prospective, cross-sectional study conducted in the Hemodialysis Center in Khartoum Teaching Hospital from September to November 2010. The study population was 100 adult patients who required hemodialysis through central venous catheter.

**Results:** Internal jugular and femoral veins were used for dialysis access in 83 and 17 patients respectively. Forty five percent of the patients developed complications. Femoral vein was more likely to be associated with infectious complications: 12 out of 17 (70.6%) (P=0,001). Diabetes was a statistically significant predictive factor for the development of complications (P = 0.014).

**Conclusion:** The use of temporary femoral catheter was considerable. The frequency of the development of complications is increasing. Femoral line and diabetes mellitus were important factors for the development of catheter-related complications.

## Introduction

Hemodialysis (HD) is associated with considerable morbidity and mortality. Infections account for approximately 15% of all deaths in this population [(1)]. Despite the efforts to secure permanent access early, catheters remain an essential access to a large number of the hemodialysis patients [(2)]. Tunnelled-cuffed HD catheters are used for long-term vascular access in a small proportion of patients mostly because opportunities for an arteriovenous access are exhausted. However, a significant number of patients require a temporary vascular access because of acute kidney injury; slow maturation or failure of their permanent arteriovenous access; or as bridging to transplantation or peritoneal dialysis. In these situations, un-tunneled catheters might be used.

Recent data of the Dialysis Outcome and Practice Patterns Study showed that 15–50% of patients in Europe and 60% of patients in the US start hemodialysis treatment with catheter as a primary access [(3)]. The major complications of hemodialysis catheters are infection; thrombosis; and malfunction. Marcel et al found that hospitalization rate of patients with un-tunneled catheter was high and it was an independent risk factor for an adverse outcome. The rate of premature removal was higher in un-tunneled femoral catheters, un-tunnelled jugular catheters and tunneled catheter respectively. It is recommended that tunneled catheters should be used whenever it can be foreseen that a hemodialysis catheter is needed for more than 14 days. [(4)]

Currently there is a perception of high rate of HD catheter-related complications in Khartoum Teaching Hospital Dialysis Center.

## Objectives

The objectives of this study were to identify central venous catheter-related complications in Khartoum Teaching Hospital Dialysis Centre and to determine factors associated with increased risk of catheter-related complications.

## Study design

This was a hospital-based, prospective, cross-sectional study conducted in Khartoum Teaching Hospital Dialysis Center during September to November 2010. One hundred adult patients who required HD through central venous catheter were enrolled. Patients who had a haemodialysis catheter placed were included. Recruitment was an ongoing process throughout the duration of the study. Patients were enrolled based on their presentation and were subsequently followed-up. The data was collected by the co-investigator from patient's records. Personal, demographic, clinical and technical (catheter- related) data were registered. The end-points were death or removal of the catheter.

Probable catheter-related sepsis was defined as significant fever >38.5 C° in a patient with HD catheter for at least 48 hours in the absence of other obvious etiological causes.

End-Stage Renal Disease (ESRD) was diagnosed based on biochemical renal failure and finding bilaterally small contracted kidneys on imaging.

Acute dialysis was defined as a need for dialysis within 48 hours from admission.

Initially the protocol was approved by the Research Committee at Sudan Medical Specialization Board. Written permission was obtained from the Director of Khartoum Teaching Hospital Dialysis Center. Informed consent was taken from the participants. Data was analyzed using computer software. Frequency tables were generated using SPSS program. Continuous data was analyzed using student's t-test and categorical data were analyzed using the chi- square test. The significance levels were set as P less than 0.05.

## Results

The study population was 100 patients and the number of catheters were 100, each patient had a single catheter during the study period. Eighteen catheters were cuffed whereas 82 were non-cuffed. Mean age of the patients was 47.73 ±16 years with two thirds (66%) being males. Hypertension and diabetes were seen in 47 and 16 patients respectively, twelve patients had both hypertension and diabetes. Nine out of sixteen (56.3%) diabetic patients developed infectious complications, whereas 33 (39.2%) out of 84 of non-diabetics developed infectious complications. The rate of infection among diabetics was found to be statistically significant (table 1) p=0.026.

End-Stage Renal Disease was the main reason for dialysis in this study (98%). Acute dialysis was performed in 84 patients. Emergency dialysis (within 12 hours of admission) was indicated in 35 patients.

The majority of the catheters: 83 (83%) were inserted into the internal jugular vein. Eighteen (21.6%) were cuffed. The mean duration of catheter utilization was 38 days. There was no significant relationship between the duration of catheter and the development of complications (P=0.08).

Forty five patients had catheter-related complications (table-2). The mean age of this group was 51 ±18 years and the mean catheter duration was 45 days. Thirty-two out of the thirty-nine infected catheters (82.1%) were of the non-cuffed type while the remaining seven (17.9%) were cuffed. Twelve of the infected catheters (28.6%) were femoral; whereas 30 (71.4%) were jugular. Within the femoral site, 12 out of 17 catheters (70.6%) were infected. The site of the catheter insertion was found to be a statistically significant predictor for the development of complications (infectious/ non-infectious (table 3) P=0.001. The majority of catheter-related sepsis (69%) occurred in combination with exit-site infection (ESI). Thirty four of the catheters were complicated by exit site infection(ESI) with mean catheter duration of 47 days.

Seventeen HD catheters were inserted in the femoral vein with a mean duration of 13.9 days. Infectious complications were found in twelve patients (70.6%) (catheter-related sepsis and exit-site infection). Deep vein thrombosis (DVT) was diagnosed in six patients by vascular flow studies. DVT alone was in two patients (11.8%) ;and DVT, with probable CRS, in four patients (23.5%).

**Table-1. Correlation between diabetes and the development of catheter-related complications.**

| | **Complications** | | | **Total** |
|---|---|---|---|---|
| | infectious complication | non-infectious complication | no complication | |
| DM | 9 (56.2%) | 2 (12.5%) | 5 (31.2%) | 16(100.0%) |
| No DM | 33 (39.3%) | 1 (1.2%) | 50 (59.5%) | 84 (100%) |
| **Total** | **42 (42%)** | **3 (3%)** | **55 (55%)** | **100 (100%)** |

DM Diabetes Mellitus
Fisher sest: P= 0.026

**Table-2. Types of Complications associated with haemodialysis catheters of the study population**

| | |
|---|---|
| CRS alone* | 7 (7%) |
| CRS +ESI** | 27 (27%) |
| ESI+/-Tunnel infection | 5 (5%) |
| Thrombosis | 6 (6%) |
| No Complication | 55 (55%) |
| **Total** | **100** |

* CRS= Catheter-related sepsis
**ESI = Exit site infection

**Table-3. Correlation between the catheter sites and development of complications**

| | | **Complications** | | | **Total** |
|---|---|---|---|---|---|
| | | Non-infectious | No complication | | |
| site of Catheter | Jugular | 30 (36.1%) | 1 (1.2%) | 52 (62.7%) | 83 (100.0%) |
| | Femoral | 12 (70.6%) | 2 (11.8%) | 3 (17.6%) | 17 (100.0%) |
| **Total** | | **42 (**42.0%) | **3** (3.0%) | **55** (55.0%) | **100** (100.0%**)** |

P = 0.001

## Discussion

In 1961 temporary HD catheter was introduced for the first time. The catheters continued to be the primary method of acute hemodialysis access [5, 6]. The incidence and risk of infection varied significantly over time and according to the site of insertion. This concept was reflected in the National Kidney Foundation Guidelines on vascular access, which recommended removal of femoral catheters after five days of use and internal jugular catheters after three weeks of use [7]. These guidelines were based on expert opinion.

In this study, ESRD was the main reason for dialysis in 98 patients (98%). All of these patients were dialyzed by temporary catheters. Acute dialysis was done in 84% of the study population. The need for acute dialysis among ESRD patients seems to be a global problem. Mendelssohn et al reported that the prevalence and incidence of temporary catheter in Canada was 33% and 70% respectively [8]. This was strikingly high despite the fact that 85% of Canadian ESRD patients had seen a nephrologist at least once before initiation of dialysis. This problem was also noted in Europe and USA with reported prevalence of 18% and 25%; and incidence of 46% and 66% respectively [8].

In UK it was reported that among patients with chronic kidney disease who required renal replacement therapy, 33% had an acute dialysis [9]. In this study the incidence of acute HD was strikingly high. Further work is needed to find out if this is related to patients, healthcare providers ,or service-related factors.

In this study, internal jugular catheters were used in 83%, but there was a high usage of femoral catheter (17%). This differs from reports by Maya et al [10] and Zaleski *et* al [11] where femoral catheters were placed in only 2%. In those studies, femoral access was used because of bilateral jugular vein occlusion. We wonder if the high rate of using femoral catheters in our study was related to patient's factors (occluded vein or bleeding risk) or doctor's factors (skills).

The study showed 36% of the catheters were removed because of infectious complications (CRS, tunnel infection or ESI). This was high compared to the 16.3% reported by Mark et al, [12], but similar to what was reported by Lukas et al, 41% [13]. Nearly half of the patients (45%) had catheter- related complications. Substantiation of catheter- related blood stream infection requires isolation of the same organism from blood and catheter tip. In this study the diagnosis of CRS was probable. We did not find a single documentation of positive blood culture. This might need to be further evaluated by another study or an audit program.

CRS was reported in jugular and femoral catheters in 69.2% and 30.8% respectively. The majority of CRS (69%) occurred in combination with ESI. ESI might be the source of contamination. Almirall et al [14] reported that three out of nine hemodialysis catheter-related blood stream infections were luminal-related. On the other hand, the rate of ESI was 34%. The majority of ESI (85.3%) was combined with CRS. The study showed that diabetes mellitus was a significant predictive factor for catheter-related infectious complications. Nine out of 16 diabetic patients had catheter-related complications p=0.014.

In the literature, there was a wide variation of blood stream infection incidence for UTCs. It was reported to be 7.6, 5.6 and 2.7 episodes/1000 catheter days for femoral, jugular and subclavian catheters respectively [15-18]. It was reported that the risk of catheter-related complications increases over time, but the threshold at which this happens is not determined [10].

In addition to a high rate of infectious complications associated with femoral catheters, we observed a high frequency of deep vein thrombosis. Almost one third : 6 out of 17 (35.3%) of the patients had DVT in this study which was higher than the 14% and 25% reported in a retrospective study by Zaleski et al[11] and Maya et al respectively[10]. The real frequency of DVT might be underestimated since diagnostic ultrasound was only done in symptomatic patients. Two-thirds of patients with DVT were suspected to have CRS. The diagnosis

of CRS could be confounded by the lack of blood culture; plus the fact that DVT can lead to systemic inflammatory response.

Limitations: Some of the limitations of this study are the small sample size and the lack of blood culture reduce the certainty of CRS.

## Conclusion

In this study the use of temporary hemodialysis catheter was considerable in terms of number and duration particularly the femoral line. The frequency of the development of complications is increasing and calls for further investigation and implementation of effective measures. Femoral line was an important and avoidable risk factor unless there were compelling reasons. Since most of the patients had ESRD, it would have been prudent if a permanent access was planned in advance through an effective primary nephrology care unit.

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# Physicians' knowledge of and commitment to the national protocol for acute rheumatic fever and rheumatic heart disease management in Khartoum.

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## Abstract

**Background:** Rheumatic Heart Disease (RHD) imposes a significant health problem in Sudan. Guidelines for management of rheumatic fever (RF) and rheumatic heart disease (RHD) have been introduced and workshops for physicians were conducted recently. Health professionals' practices are key elements in achieving implementation of a comprehensive program for controlling RHD. This study was conducted to assess the physicians' knowledge of, and adherence to, the implementation of the national protocol for control of RF and RHD.

**Methods:** The study was a descriptive, cross-sectional, facility- based survey carried- out in three main hospitals in Khartoum State in the period from July to October 2015, involving physicians of different professional levels and junior doctors working in the paediatric units. A structured pre-coded questionnaire focussing on awareness and adherence to the national guidelines was used. A scoring system for the physicians' adherence was set and data were analysed using SPSS software version 20.0.

**Results:** A total of 140 participants responded to the questionnaire (78% response rate): 10 paediatric physicians, 68 paediatric registrars, and 62 junior doctors. Of these, 53.6% were not aware of the existence of a national protocol for the management of RHD. Of the total 65respondents aware of the existence of the protocol, 60 (92.3%) believed that the protocol provided appropriate measures for the control of RHD. Adherence scoring showed that 19% had poor adherence; 50% had an average adherence and about 31% had a high adherence score. Benzathine penicillin G (BPG) was not available in the emergency department at any of the three hospitals.

**Conclusion:** The study identified gaps in physicians' knowledge of ,and adherence to, the RHD Control Program. There is a need to consolidate training programs especially for junior doctors and to provide BPG in the emergency departments.

## Introduction

Rheumatic heart disease (RHD) is a devastating sequel of acute rheumatic fever (ARF), initiated by a simple throat infection with group A streptococcus in susceptible population. It is the predominant cause of acquired heart disease in young people all over the world. It is highly prevalent in Sudan with an estimated prevalence of 10 in 1000.[1]Sudanese patients present with severe lesions needing surgical intervention which is affordable for few patients.[2]Prevention of RHD needs to be implemented.

**RHD Control Program** was initiated in Sudan in 2012 by a Working Group on Paediatric Cardiology and the Sudan Heart Society together with the Sudanese Association of Paediatricians and was approved by the Ministry of Health (MOH). It was based on: increasing public Awareness, Surveillance, Advocacy and introducing primary and consolidating secondary Prevention (A.S.A.P.).[3]It was adopted from the program endorsed at the 1st All Africa Workshop on Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) held in South

Africa in October 2005.[4]

Although approved by the Sudan Ministry of Health (MOH), the program did not have a dedicated fund or administrative assistance from the ministry. All the paper and field work have been executed through voluntary and charity work led by the National Committee of RHD Control.

Evaluating adherence of physicians to the program guidelines will help to evaluate the efficacy of training and reveal any deficiencies that need to be addressed.

## Methodology

A descriptive, cross-sectional, facility-based survey was conducted in three paediatric departments in Khartoum: at Ahmed Gassim Hospital (AGH), Ibrahim Malik Teaching Hospital(IMTH) and Omdurman Paediatric Hospital(OPH) in the period from July to October 2015.Paediatric Physicians and junior doctors affiliated to the paediatric units and medical directors of paediatric emergency departments of the three hospitals were included.

The data were collected using a structured questionnaireconsisting of two parts. The first part covered the demographic characteristics of participants (professional degree and affiliated hospital) and the second part assessed the awareness of physicians regarding the national protocol for RF/RHD (awareness of existence of the protocol, first time to become familiar with it, source of knowledge and the participants' opinion about the protocol) and the adherence of participants to the priority issues in the guidelines: (i) diagnosis of Bacterial pharyngitis (B.P.) depending on the clinical criteria; (ii) full management of B.P.; (iii) detection of RF cases depending on the revised Jon's criteria; (iv) full management of RF; (v) notification of ARF and (vi) BPG injection measures and precautions.

The questionnaire was pre-coded. The answers were graded (out of 9) and a scoring system for the adherence was established as follows: participants scoring (0-3) were considered to have "poor adherence"; those who scored (4-6) were considered to have "average adherence" and the scores (7-9) represented "high adherence".

A written permission was obtained from the administration in each of the three hospitals and verbal consents were taken from the participants.

For data analysis SPSS (Statistical Package for Social Sciences) software (version 20.0) was used and descriptive statistics were computed for data presentation. Statistical test (Chi-square test) was used to describe relation between categorical variables and the level of significance was set at ($P < 0.05$).

## Results

A total of 140 participants responded to the questionnaire. Regarding their professional degree 9 (6.4%) of them were consultant paediatricians, 1 (0.7%) paediatric specialist, 68 (48.6%) paediatric registrars, 11 (7.9%) medical officers, and 51 (36.4%) house officers working in the paediatric units distributed in the three hospitals as shown in figure 1.

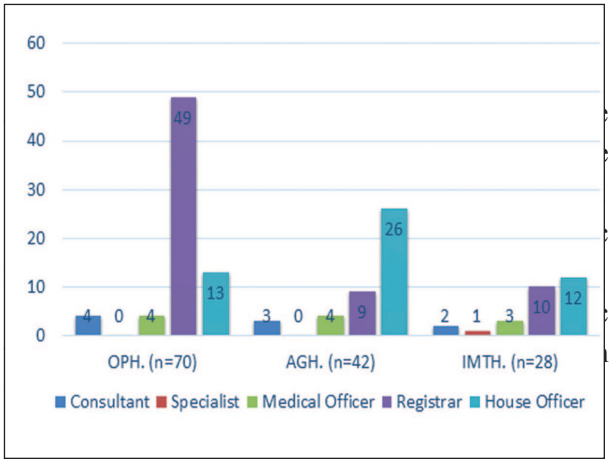


**Figure 1. Professional levels of participants**

Sixty-five (46.4%) of the participants were aware of the existence of a national protocol for RHD and the remaining 53.6% were not. The most frequent source of knowledge about the protocol was a senior colleague (49.2%). (Table 1)

**Table 1. Awareness of the participants about the national protocol for control of RF/RHD**

| Awareness of physicians | | n | % |
|---|---|---|---|
| Awareness of the existence of the national protocol | Yes | 65 | 46.4% |
| | No | 75 | 53.6% |
| Duration of knowledge about the protocol | 1 - 6 months | 16 | 24.6% |
| | 7 months - 1 year | 12 | 18.5% |
| | More than a year | 37 | 56.9% |
| Source of knowledge | Trainings and workshops | 23 | 35.4% |
| | Manuals | 6 | 9.2% |
| | Senior Doctor or colleague | 32 | 49.2% |
| | Others | 4 | 6.2% |
| Physicians` belief about the protocol | Yes the protocol provides appropriate measures for the control of RF/RHD | 60 | 92.3% |
| | No the protocol doesn`t provide appropriate measures for the control of RF/RHD | 5 | 7.7% |

Sixty (92.3%) of the total 65 participants who were aware of the protocol believed that the protocol provides appropriate measures for the control of RHD.

Adherence scoring showed that 19.3% had a poor adherence score, 50% had an average adherence score and 30.7% had a high adherence score. (Table 2)

**Table 2. Adherence scores of the participants to the national protocol for control of RF/RHD**

| Adherence score | n | % |
|---|---|---|
| Poor Adherence | 27 | 19.3 |
| Average Adherence | 70 | 50.0 |
| High Adherence | 43 | 30.7 |
| Total | 140 | 100.0 |

Consultants and registrars reported high levels of adherence and the lowest levels were reported among junior doctors (house-officers), indicating a positive correlation between the level of adherence and the professional degree ($P < 0.05$).

There was also a positive correlation between the participants' awareness of the protocol and their level of adherence ($p < 0.05$).

Participants from (AGH) had the lowest adherence level sand participants from (OPH) showed high levels of adherence.

Benzathine penicillin G (BPG) was not available in the emergency department at any of the three hospitals.

## Discussion

This study included pediatricians and doctors working in pediatric departments in three hospitals, encountering cases of ARF and RHD. Seventy-five participants (53.6%) were not aware of the existence of the national protocol for the control of RHD. Of the sixty-five who were aware of its existence 33 (49.2%) learned about its existence from senior colleagues and not from publication of guidelines. Low levels of awareness and adherence

were noted mainly among junior doctors. Twenty-seven participants (19.3%) showed poor adherence. These facts reflect clearly shortcomings in the implementation and dissemination of information relevant to the national program.

The results of awareness and adherence to the program are similar to published data from South Africa.[5] They are, however, below the figures reported from the Netherlands where most of the doctors (93%) were found to be well- informed about the guidelines and widely accepting them. The sources of information and guidelines in the Netherlands were the scientific journals for most of the respondents (85%).[6]many guidelines are not used after dissemination. Implementation activities frequently produce only moderate improvement. It is important to study specific guideline programs in detail to learn from their successes and failures. OBJECTIVES: Experiences with more than 10 years of development and dissemination of clinical guidelines for family medicine in the Netherlands are presented in this paper. RESULTS: More than 70 evidence-based guidelines have been set in a rigorous procedure and have been spread via a variety of strategies. Knowledge and acceptance of the guidelines in the target group is high. In particular, a multifaceted approach with written (scientific journal, support materials

The overall results of the study concerning awareness and adherence to the program are not satisfactory. This is probably expected in the absence of proper implementation and dissemination of relevant information while the guidelines were published only in 2015.[7] Nevertheless, seventy participants (50%) had average adherence and forty-three others (30.7%) had high levels of adherence. Moreover, the fact that the participants who were aware of the program (n = 65) accepted and believed that the program provided appropriate measures to control RHD is encouraging.

If more efforts are injected into the program by all concerned i.e. The Ministry of Health, the Sudan Heart Society, the Sudanese Association of Pediatricians, educational and training Institutes and the various charity and voluntary groups, the outcome will certainly improve and this will contribute to the success of the project as it had contributed to its success in other parts of the world such as Cuba.[6]many guidelines are not used after dissemination. Implementation activities frequently produce only moderate improvement. It is important to study specific guideline programs in detail to learn from their successes and failures. OBJECTIVES: Experiences with more than 10 years of development and dissemination of clinical guidelines for family medicine in the Netherlands are presented in this paper. RESULTS: More than 70 evidence-based guidelines have been set in a rigorous procedure and have been spread via a variety of strategies. Knowledge and acceptance of the guidelines in the target group is high. In particular, a multifaceted approach with written (scientific journal, support materials-[8]

Benzathine penicillin G is the antibiotic of choice in the treatment of B.P, treatment of ARF and as secondary prophylaxis for RHD. It was ,unfortunately. unavailable in the pediatric emergency department at any of the three hospitals studied and its unavailability will certainly result in a great threat of increased and uncontrolled occurrence of RF and RHD.[9]there is no agreement on the most effective method of giving penicillin. OBJECTIVES: To assess the effects of penicillin compared to placebo and the effects of different penicillin regimens and formulations for preventing streptococcal infection and rheumatic fever recurrence. SEARCH STRATEGY: We searched the Controlled Trials Register (Cochrane Library Issue 2, 2001-[10] Non-provision of BPG in the pediatric emergency departments is a serious shortcoming in the implementation and will defeat the expected outcome of the comprehensive program for control of RHD.

## Conclusion

Benzathine penicillin G was unavailable in any of the three hospitals studied. Its unavailability is a serious shortcoming that should be urgently addressed by the program administrators and BPG should be made available in the hospitals. The

study also revealed gaps in the implementation of the national program for control of RHD both in the awareness and the adherence aspects, which were more apparent in younger doctors. There is a need to consolidate the current training programs at regular time intervals with special emphasis to the new comers to the system.

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