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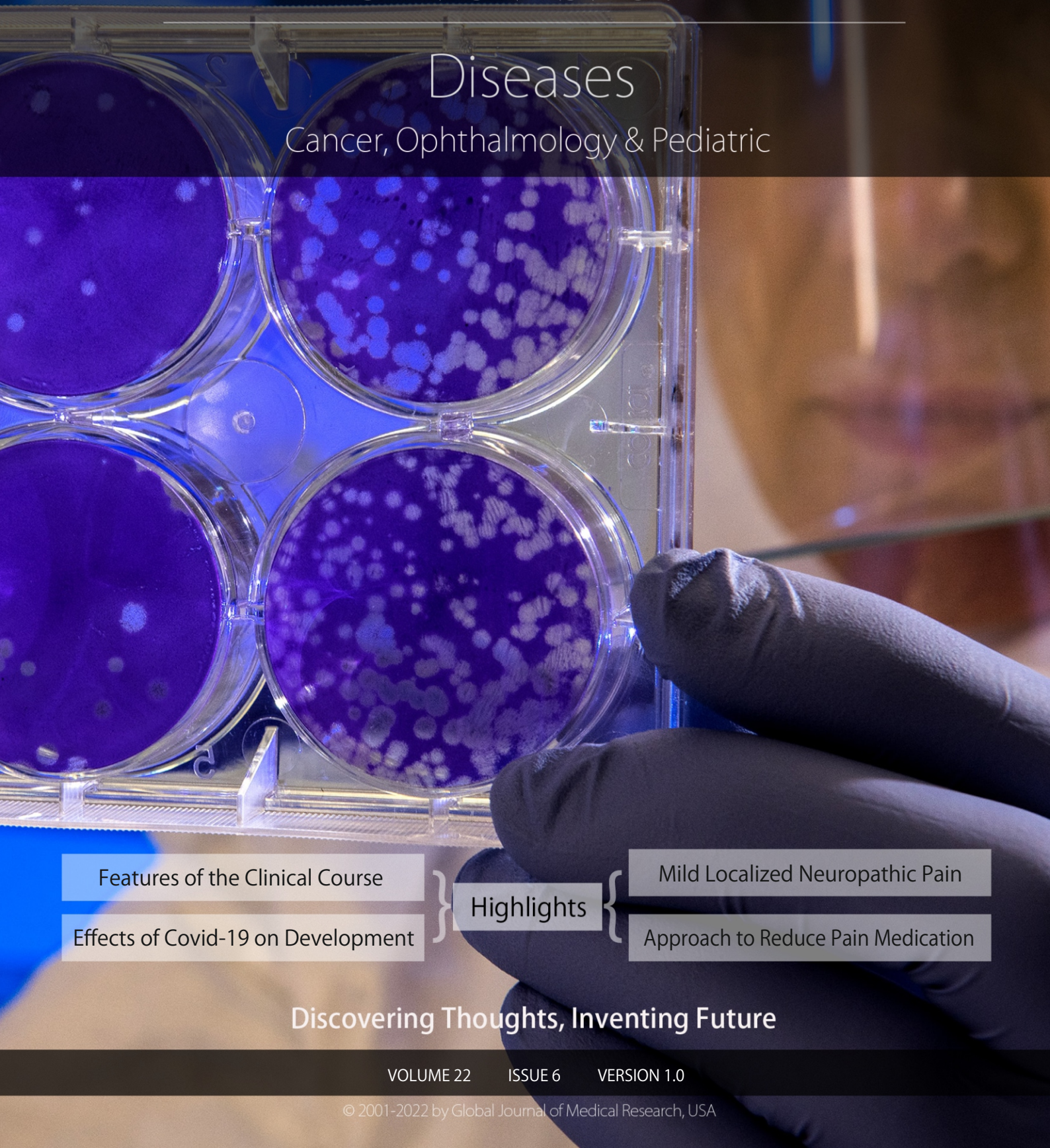

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Highlights

Mild Localized Neuropathic Pain

Approach to Reduce Pain Medication

Discovering Thoughts, Inventing Future

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Intradermal Glucose 5% Injections for Mild Localized Neuropathic Pain- A New Approach to Reduce Pain Medication

By Jan Kersschot

Abstract- As localized neuropathic pain can seriously decrease quality of life, physicians are challenged to look for treatment modalities which are easy to apply, safe and effective. Over the last decade, isotonic glucose (or dextrose) injections have received more attention among clinicians worldwide. In this article, the focus is on the application of intradermal injections of glucose 5%. Glucopuncture is especially interesting for doctors and patients who live in remote areas where pain medications are not available, or too expensive.

Keywords: localized neuropathic pain, glucopuncture, allodynia, intracutaneous injection.

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Intradermal Glucose 5% Injections for Mild Localized Neuropathic Pain- A New Approach to Reduce Pain Medication

Jan Kersschot

Abstract- As localized neuropathic pain can seriously decrease quality of life, physicians are challenged to look for treatment modalities which are easy to apply, safe and effective. Over the last decade, isotonic glucose (or dextrose) injections have received more attention among clinicians worldwide. In this article, the focus is on the application of intradermal injections of glucose 5%. Glucopuncture is especially interesting for doctors and patients who live in remote areas where pain medications are not available, or too expensive.

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I. Neuropathic pain

Nerves are usually viewed as simple conduits of electrical signals to make muscles move and enable sensation of pain, temperature and pressure. However, axons within nerves, also known as nervi nervorum, are also capable of reacting to their immediate environment, such as to mechanical pressure or to direct injury from trauma.

Nociceptors are sensory neurons that detect harmful stimuli, and can become sensitized after infection (e.g., herpes), direct injury, surgery [i,ii] or repetitive overstimulation. When nociceptors are sensitized, they often exhibit spontaneous activity in the absence of stimulation, called “ongoing activity” [iii]. Because of their very specialized anatomy and physiology, nerves are capable of creating or mediating certain types of (chronic) pain [iv]. It has been made clear that nociceptor neurons also release neuropeptides and neurotransmitters from nerve terminals which can regulate adaptive immune cell responses [v]. Macrophages can activate nociceptors and nociceptors can secrete neuropeptides and chemokines which act on macrophages; in chronic pain these bilateral macrophage-nociceptor interactions are mediated by microRNAs and microRNA-containing exosomes [vi].

Neuropathic pain (NP) is described as a (superficial) pain arising as a direct consequence of a lesion or disease affecting the somatosensory system at the peripheral or central level [vii]. It affects about 10% of the world population [viii, ix]. Despite the progress in pain management methods made over the last decades, neuropathic pain significantly impacts patients’ quality of life. Both pharmacological and non-pharmacological methods often fail to reduce the pain or may induce serious side effects. Neuropathic pain resulting from diabetes or chemotherapy are not considered as a subject of this article.

Diverse causes of neuropathic pain are associated with excessive inflammation in both the peripheral and central nervous system which may contribute to the initiation and even maintenance of persistent pain [x]. Chemical mediators, such as cytokines, released during an inflammatory response have the undesired side effect of sensitizing or stimulating nociceptors. These changes can promote long-term persistent neuropathic pain. Transient receptor potential vanilloid channel 1 (TRPV1), a nonselective cation channel, has been shown to play an important role in neuropathic pain (xi). It has been found that IL-6 and IL-1beta also play a role in pain induced by perineural inflammation [xii]. All this may explain why sometimes a minor trauma can lead to extreme sensitivity to touch (allodynia) and severe chronic neuropathic pain.

II. Localized Neuropathic Pain

In more than half of cases of NP, the pain is localized and affects a certain area of the body [xiii]. This article focusses on this peripheral or localized type of neuropathic pain. Localized neuropathic pain (LNP) is characterized by circumscribed areas of pain with abnormal skin sensitivity or spontaneous burning pain with no obvious cause.

It is hypothesized that even a minor peripheral nerve injury can induce functional and structural changes in neuronal cells. These functional and structural changes release numerous signaling molecules in response to the nerve damage. As these mediators modulate corresponding receptors on cell membranes, such interactions can create vicious circles of complaints such as burning pain and allodynia. These maladaptive mechanisms contribute to further sensitization of peripheral nerve endings [xiv]. It is hypothesized that noxious stimuli stimulate peripheral nerves to release calcitonin gene-related peptide

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(CGRP) and prostaglandin E2 (PGE2) [xv]. Interleukin-1beta also seems to play a role in neuropathic pain [xvi, xvii].

III. Differential Diagnosis

LNP needs to be differentiated from complex regional pain syndrome (CRPS) which is a difficult-to-treat chronic pain condition [xviii]. CRPS often involves hyperalgesia and allodynia of the extremities and on top of that there is autonomic nervous system involvement. CRPS is not an indication for Glucopuncture. Neither can neuropathic pain resulting from nerve compression, autoimmune disease, diabetes [xix] or chemotherapy be treated with Glucopuncture.

IV. Regional Treatments for Localized Neuropathic Pain

The standard treatment of LNP is antidepressants and anticonvulsants [xx]. Regional treatments such as patches and injections are gaining popularity in the local management of peripheral neuropathic pain. A major advantage of transdermal treatments is that they may reduce the risk of adverse events that are often associated with systemic medication. Topical modalities may be used in combination with oral drugs resulting in less drug-drug interactions.

Topical treatments such as 5 % lidocaine patches and 8 % capsaicin patches have been used in several LNP models [xxi, xxii, xxiii]. In this article, the focus will solely be on local intradermal injections with glucose 5%. Typically, 1 mL of solution is injected per cm (half inch) of the symptomatic area. Positive feedback of patients treated with this new technique has encouraged certain clinicians to present it as a new approach to treat mild forms of LNP. The new term Glucopuncture is introduced to raise awareness about these injections among both doctors and patients. However, no randomized clinical trials have illustrated its safety or efficacy yet. This technique is especially interesting for physicians who work in remote areas where modern diagnostic and therapeutic modalities are not available, or too expensive for their patients.

V. Glucopuncture for Mild Localized Neuropathic Pain

As pointed out earlier, first-line pharmacological treatments for LNP include pain medication, antidepressants and anticonvulsants such as gabapentin and pregabalin [xxiv]. However, some patients complain about side effects of such medication. Others obviously overuse pain medication. One of the goals of Glucopuncture is to reduce the use of systemic medication by giving a series of glucose 5% injections intradermally. Best results are achieved when the injections are started in the beginning of the disease before the somatosensory system is affected at central level. Instead of giving intradermal injections, one can also give the glucose perineurally [xxv, xxvi, xxvii] but this technique is not a topic of this article. Clinical randomized studies are required to see which dose, frequency and injection technique works best for mild LNP.

VI. Definition of Glucopuncture

Glucopuncture (GP) is an easy-to-learn procedure which can be done in a small private practice without ultrasound guidance. GP is defined as an injection-based therapy for the management of a variety of musculoskeletal conditions [xxviii]. In general, glucose 5% in water (G5W) injections are given in dermis, muscles, fascia, tendons and ligaments. No local anesthetics nor corticosteroids are added. When treating localized neuropathic pain, multiple intracutaneous injections with G5W in the zone of pain referral are advised. The treatment is repeated once a week to once every two weeks. After a series of sessions, the pain modulation can last up to several months. If no major improvement is noticed after five sessions, the treatment is stopped.

VII. Glucose Metabolism in Brain Cortex

The human brain depends upon glucose as its main source of energy, and glucose metabolism is critical for brain physiology [xxix, xxx]. The brain accounts for about 2% of the body weight, yet it consumes about 20% of glucose-derived energy [xxxi]. Glucose metabolism provides the fuel for physiological brain function through the generation of ATP, the foundation for neuronal and non-neuronal cellular maintenance [xxxii]. Therefore, regulation of glucose metabolism is critical for cortex physiology [xxxiii]. The largest proportion of energy in the brain is consumed for neuronal computation and information processing [xxxiv], e.g., the generation of action potentials and postsynaptic potentials generated after synaptic events, and the maintenance of ion gradients and neuronal resting potential [xxxv]. Additionally, glucose metabolism provides the energy and precursors for the biosynthesis of neurotransmitters [xxxvi]. The question is whether glucose is equally important for the peripheral nervous system as it is for the brain. This question has not been answered yet, but further exploration of this issue might explain the clinical effects which are noticed when injecting isotonic glucose perineurally (e.g., carpal tunnel) or intradermally. It is clear that when glucose is applied to a patient systemically, for example, as an IV infusion, there are no pain modulating effects at all. This means that in the search for the exact mode of action of Glucopuncture, the scientific community needs to focus

on what exactly is happening when the glucose arrives directly in the extracellular matrix (ECM). In other words, the mechanisms of action of glucose as found in lab tests (*in vitro*) or hypotheses from diabetic research provide only limited value.

VIII. Working Hypothesis of Glucopuncture

Glucose is a crucial energy source for cellular health. The goal of Glucopuncture is to deliver additional glucose in the extracellular space to support directly cellular ATP production. Hypertonic solutions are not advised because they lead to osmotic destruction of the cells. When glucose is injected into the body, it arrives in the extracellular matrix (ECM). Then, the glucose is transported across the cell membrane [xxxvii].

a) *The Effect of Glucose on Dermal Sensory Nociceptors*

Nociceptors are sensory neurons that detect harmful stimuli, and can become sensitized following injury or repetitive stimulation. When sensitized, nociceptors often exhibit spontaneous activity in the absence of apparent stimulation [xxxviii]. Sensory receptors are found in dermis, muscles, fascia, tendons and ligaments [xxxix]. These receptors include mechanoreceptors, nociceptors, and thermoreceptors [xl, xli]. Especially dermal nociceptors [xlii, xliii, xliv] are important to explain the pain modulating effects of intradermal glucose injections. And this is very likely the most important mechanism when treating regional neuralgia [xlv]. The transient receptor potential ankyrin1 (TRPA1), a member of the TRP channels, acts as 'polymodal cellular sensor' on primary sensory neurons where it mediates the peripheral and central processing of pain [xlvi].

b) *ATP as a Pain Modulator*

ATP may play a direct role in pain modulation, especially when dealing with peripheral nerves. It has been illustrated that ATP injection increases expression of several markers for regenerative activity in sensory neurons, including phospho-STAT3 and GAP43 [xlvii]. It has been found that ATP infusion improves spontaneous pain and tactile allodynia [xlviii, xlix] in patients with (postherpetic) neuralgia. It also became clear that it works for neuropathic orofacial pain, but not for other types of orofacial pain, indicating that the neuropathic element seems to be an important factor in the effects of ATP [l]. These studies might indicate that glucose may have its pain modulating effects on neuropathic pain via ATP [li]. More research in this field may confirm the anecdotal information available so far.

IX. History of Glucopuncture

Subcutaneous injections with glucose 5% were first described in the treatment of Achilles tendinopathy [lii]. Later on, glucose 5% injections were used to treat other forms of musculoskeletal pain [liii, liv, lv]. Some physicians also used glucose 5% injections for tennis elbow [lvi], tension headache, postherpetic neuralgia, and Dupuytren's stage 1. As the total amount of glucose is very small (similar to eating a few strawberries once a week), glucopuncture can be applied for patients who are diabetic or those who are on a strict calorie diet.

X. Difference Between Glucopuncture and Prolotherapy

Glucose and dextrose injections have been used for several decades in prolotherapy [lvii, lviii, lix, lx, lxi, lxii, lxiii, lxiv]. Prolotherapy injects hypertonic dextrose (10% net concentration or more) into, for example, entheses of ligaments, bands and tendons. Injections into periost and into joint cavities are also given. Hyperosmolar solutions lead to localized cell shrinking and subsequent cell destruction. This phenomenon creates release of arachidonic acid (from the cell membrane) which creates a local inflammatory reaction. The latter may lead to local tissue proliferation – hence the description prolotherapy - and even formation of scar tissue [lxv]. Local anesthetics are always added to make the injections less painful.

Glucopuncture also injects glucose (or dextrose) but only in an isotonic concentration (5%). As a result, there is no local osmotic shock, no cell death, no subsequent inflammatory reaction. That is why the ATP hypothesis was required to explain the pain modulating effects of glucopuncture, as well as the positive effect of glucose 5% injections on tissue repair (as in Dupuytren's stage 1). The injection techniques are also different. Glucopuncture typically uses more shallow injections than prolotherapy. Most of the injections are given in the dermis, and also in trigger points of muscles and ligaments. In contrast to prolotherapy, local anesthetics are never added to the solution (Table 1).

XI. Intradermal Glucose 5% Injections for Localized Neuropathic Pain

During questioning, the patient is asked to point out the zone of pain referral. Sometimes the physician can localize pain points within the pain region which are extra sore. Such points may receive an extra dose of injectate. The treatment itself is remarkably simple and straightforward. The injection procedure itself typically takes less than a minute to perform. After identifying the tender zone, one gives multiple intradermal injections (intracutaneous wheals) with glucose 5% in the pain region, as indicated by the patient. Intracutaneous injections usually feel like sharp stings for a few seconds. Intracutaneous injections (IC) are more painful than subcutaneous injections (SC) but IC injections seem to be more effective regarding modulation of

neuropathic pain. Some patients have a very thin epidermis, which makes IC injections impossible, so one has to rely on SC injections instead. The injections are usually given 1 cm apart. About 0.5 to 1 mL is given in each spot with a 30 G or 27 G needle. The total volume per session is usually between 2 and 20 mL, depending on the size of the tender region. It often happens that the patient experiences immediate pain relief a few seconds or minutes after the glucose 5% injections. This is rather surprising, as no local anesthetics are added to the glucose. Unfortunately, this pain modulating effect of glucose 5% lasts only for a few hours to a few days. In some patients, the symptomatic improvement only becomes apparent after the second or third session. To obtain long term results, repetition is required until lasting pain relief has been achieved.

XII. Conclusion

In the search for treatment modalities which are safe, affordable and effective, several clinicians worldwide have experienced that glucose 5% injections are an inexpensive treatment to reduce their patient's intake of pain medication. This is especially true for mild forms of regional neuropathic pain. More research in this field may confirm their clinical findings.

Table-1

Difference PT and GP	Prolotherapy	Glucopuncture
What?		
Hypertonic Glucose	x	
Local Anesthetics	x	
Glucose 5% in Water		x
Where?		
ID		x
IM		x
IL	x	x
IA	x	
How?		
Osmotic Shock	x	
Proliferation	x	
ATP Production	x	x
TRPV1 (Needle Effect)	x	x

Table: Difference between PT (Prolotherapy) and GP (Glucopuncture). ID: Intradermal. IM: intramuscular, IL: intraligamentous, IA: intraarticular

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The Effects of Covid-19 on Development of Deep Venous Thrombosis: Bibliographic Review

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Abstract- The new coronavirus 2019 (COVID-19) is clinically characterized by the multisystemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), whose symptoms and prognosis depend on the stage of the disease in which the patient is. In aggravating cases, it is necessary to use mechanical ventilation or treatment in intensive care units (ICU), taking into account the high risk of mortality. Although the fundamental clinical features of the disease are respiratory, neurological, renal, digestive, cardiac and other organ complications also exist. The work in question, given the volume of clinical trials, seeks to effectively investigate potential therapies for COVID-19, highlighting the need to produce high-quality evidence. In addition, the biological plausibility of the thrombotic risk in SARS-CoV-2 and its cardiac involvement due to the exacerbated inflammatory response and due to pre-existing manifestations or due to acquired manifestations was discussed.

Keywords: *covid-19; sars-cov-2; deep vein thrombosis; coagulation.*

GJMR-F Classification: *DDC Code: 616.2 LCC Code: RC776.S27*

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The Effects of Covid-19 on Development of Deep Venous Thrombosis: Bibliographic Review

Os Efeitos Da Covid-19 No Desenvolvimento De Trombose Venosa Profunda: Revisão Bibliográfica

Luiz Ferreira da Silva [α], Bruna Katharine Cavalcante Nascimento [σ], Caroline Augusta Bezerra Xavier [ρ] Thereza karolina Brissow Pinheiro [ω] & Victor Mota Maciel [¥]

Resumo- O novo coronavírus 2019 (COVID-19) é clinicamente caracterizado pela síndrome respiratória aguda grave coronavírus 2 (SARS-CoV-2), multissistêmica, cujos sintomas e prognósticos dependem da fase da doença em que o paciente se encontra. Sendo que, em casos agravantes, torna-se necessária a utilização de ventilação mecânica ou tratamento em unidades de terapia intensiva (UTI), levando em consideração o elevado risco de mortalidade. Embora as características clínicas fundamentais da doença sejam respiratórias, também existem complicações neurológicas, renais, digestivas, cardíacas e em outros órgãos. O trabalho em questão, em vista do volume dos ensaios clínicos, procura investigar efetivamente terapias potenciais para COVID-19, destacando a necessidade de produzir evidências de alta qualidade. Além disso, foi discutida a plausibilidade biológica do risco trombótico na SARS-CoV-2 e seus envolvimentos cardíacos mediante à resposta inflamatória exacerbada e devido às manifestações pré-existentes ou em decorrência das manifestações adquiridas. Portanto, realizou-se uma revisão sistemática da literatura, relatando medidas para avaliar as alterações detectáveis neste cenário e sua relação com a gravidade clínica.

Palavras-Chave: *covid-19; sars-cov-2; deep vein thrombosis; coagulação.*

Abstract- The new coronavirus 2019 (COVID-19) is clinically characterized by the multisystemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), whose symptoms and prognosis depend on the stage of the disease in which the patient is. In aggravating cases, it is necessary to use mechanical ventilation or treatment in intensive care units (ICU), taking into account the high risk of mortality. Although the fundamental clinical features of the disease are respiratory, neurological, renal, digestive, cardiac and other organ complications also exist. The work in question, given the volume of clinical trials, seeks to effectively investigate potential therapies for COVID-19, highlighting the need to produce high-quality evidence. In addition, the biological plausibility of the thrombotic risk in SARS-CoV-2 and its cardiac involvement due to the exacerbated inflammatory response and due to pre-existing manifestations or due to acquired manifestations was discussed. Therefore, we carried out a systematic review of the literature, reporting measures to assess detectable changes in this scenario and their relationship with clinical severity.

Keywords: *covid-19; sars-cov-2; deep vein thrombosis; coagulation.*

I. Introdução

A COVID-19 trata-se de uma enfermidade resultante de um novo tipo de coronavírus, denominado oficialmente como Síndrome Respiratória Aguda Grave-Coronavírus-2 (SARS-CoV-2), que resulta em manifestações clínicas em diferentes regiões do corpo humano. Surgiu inicialmente na China, em dezembro de 2019, e disseminou-se rapidamente em todo o mundo(SARZI-PUTTINI et al., 2020).

A maior parte da população que é infectada pelo SARS-CoV-2 demonstra sintomas leves e moderados, porém, a outra parte das pessoas acometidas apresentam características mais severas, que agridem não somente o sistema respiratório, mas também podem afetar o sistema digestório, renal, circulatório e nervoso. Esse estágio mais severo da doença pode culminar na falência de vários órgãos e evoluir para a morte do paciente (BRANDÃO et al., 2020).A transmissão da COVID-19, de acordo com alguns estudos, por uma pessoa infectada pelo vírus ocorre no período sintomático da doença, que tem tempo médio de 14 dias a partir do contágio, no entanto, essa transmissão pode

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acontecer também por meio de pessoas assintomáticas, mas isso não é algo totalmente definido (MINISTÉRIO DA SAÚDE, 2020).

A fase I da doença, que é sua forma leve, normalmente se apresenta pela presença de sinais e sintomas de uma síndrome gripal, como coriza, febre, tosse seca, diarreia, mialgia, cefaleia e distúrbios olfativos ou do paladar (anosmia ou ageusia). Já a fase II, que é a forma moderada, se caracteriza por dispneia, queda na saturação de oxigênio, desconforto respiratório e piora das condições clínicas de base. Enquanto que a fase III, forma grave, demonstra sinais e sintomas como choque e insuficiência/falência respiratória (MINISTÉRIO DA SAÚDE, 2020).

Na fase III, estágio mais avançado da doença, também caracterizada como fase hiperinflamatória, a doença passa a ser chamada de LHHs (LinfoHistiocitose Hemofagocítica secundária), que é uma síndrome de inflamação que acomete tanto o pulmão como também o restante do organismo (BRANDÃO et al., 2020). "A LHHs se caracteriza por hiperativação imunológica devido a não eliminação adequada de macrófagos ativados pelas células NK e os linfócitos T citotóxicos, resultando em produção excessiva de citocinas pró-inflamatórias" (BRANDÃO et al., 2020). Ou seja, na fase III, tem-se uma resposta imune desregulada, com uma enorme quantidade de citocinas circulantes e um excesso de atividade dos mecanismos inflamatórios, e isso pode levar à morte do paciente(FARIA et al., 2020).

A fim de penetrar a célula, o SARS-CoV-2 utiliza sua proteína viral estrutural spike (S) que se liga ao receptor da enzima conversora de angiotensina 2 (ACE2). Após esta ligação, a partícula de vírus usa receptores e endossomos da célula hospedeira para invadir as células. Uma protease serina transmembranar tipo 2 do hospedeiro, TMPRSS2, facilita a entrada na célula através da proteína S. O vírus, então, sintetiza RNA por meio de sua RNA polimerase dependente de RNA. As proteínas estruturais são sintetizadas, levando à conclusão na montagem e liberação de partículas virais (HOFFMANN et al., 2020).

Embora o trato respiratório seja o principal alvo do SARS-CoV-2, o sistema cardiovascular pode estar envolvido de diferentes maneiras, sendo apontando como uma das maiores fontes de complicações secundárias, em virtude do surgimento clássico de insuficiência cardíaca aguda e o desafio do controle do foco infeccioso (RENTE et al., 2020).O sistema microvascular, por sua vez, apresenta-se danificado com as reações inflamatórias que proporcionam alto risco de disfunção na coagulação, manifestando-se patologicamente como vasculite generalizada de pequenos vasos e extensa microtrombose, principalmente nos pulmões, resultando em um distúrbio de ventilação e perfusão, sendo este responsável pela insuficiência respiratória hipoxêmica severa, necessitando de ventilação mecânica (GUERRA; CARBONIERI; FITTIPALDI, 2020).

Ao longo da evolução da infecção por COVID-19, a carga viral do paciente aumenta no decorrer do tempo e isso resulta em uma cadeia de acontecimentos que gera inflamação e sepse. Estes eventos acabam proporcionando a liberação de citocinas inflamatórias, as quais promovem a progressão dos níveis de trombina na circulação sistêmica (SRIVASTAVA et al., 2020). Os mecanismos que envolvem distúrbios trombóticos e sangramentos nas infecções causadas por vírus são bastante conhecidos e abrangem diversos processos envolvendo a coagulação e a rede fibrinolítica, bem como plaquetas, células endoteliais e leucócitos (KIPSHIDZE et al., 2020).

A deficiência fibrinolítica dos pacientes com infecções virais tem também como fator contribuinte o desequilíbrio dessas redes fibrinolíticas e das serinas proteases. Nesses pacientes, observou-seque o desenvolvimento de anticorpos antifosfolipídeos estavam correlacionados com a infecção viral. Esses mesmos anticorpos foram associados atualmente com os agravamentos trombóticos percebidos em pacientes com COVID-19 (KIPSHIDZE et al., 2020).

II. Metodologia

Para a elaboração desta revisão, foram selecionados 20 artigos de acordo os descritores: SARS-CoV-2; Deep Vein Thrombosis; COVID-19, na plataforma PubMed e SciHub. Posteriormente, foram selecionados 09 artigos, que de acordo com o título e objetivosabordavam intimamente a relação entre a COVID-19 e o surgimento de trombose.

III. Discussão

Segundo Tomasz etal. (2020), a doença causada pelo SARS-CoV-2, também chamada de COVID-19, afeta principalmente o sistema respiratório dos indivíduos infectados, causando pneumonite intersticial e síndrome do desconforto respiratório agudo (SDRA), no entanto, também pode afetar outros sistemas, como o sistema hepático e o cardiovascular. Essa doença causa diversas complicações no organismo, dentre elas as mais comuns são as arritmias, lesões cardíacas, miocardite fulminante, insuficiência cardíaca, embolia pulmonar e coagulação intravascular disseminada (DIC).

O SARS-CoV-2 invade as células-alvo por meio da enzima conversora de angiotensina 2 (ECA2), uma proteína de membrana integral do tipo I. Esta enzima foi instituída como o receptor hospedeiro funcional para a síndrome respiratória aguda grave do coronavírus 2 (SARS-CoV-2). A ECA2 é expressa em diversas células de diferentes órgãos do corpo humano, o que é um dos fatores determinantes para a grande variedade de sintomas apresentados pelos pacientes com a doença.

Além disso, existem fatores, tais como a idade, sexo, etnia, a presença de cardiopatias, síndrome metabólica e o uso de medicações, que estão associados à expressão alterada de ECA2, o que possui relação intrínseca com a gravidade e progressão da COVID-19 (ARNO et.al. 2020).

O vírus, ao adentrar no organismo, realiza a clivagem proteolítica de sua proteína S por uma serina protease, posteriormente, ele se liga à ECA2 e, desta forma, consegue realizar a endocitose em células que expressam esta proteína em suas membranas, como exemplo, células presentes no sistema respiratório, no sistema cardiovascular, sistema renal e sistema gastrointestinal (TOMASZ et al. 2020). Durante as fases iniciais da infecção, que cursam com uma progressão rápida, essa invasão celular disseminada induz uma resposta imunológica e inflamatória, podendo gerar uma tempestade severa de citocinas, sendo esta resposta chamada de Síndrome da Tempestade de Citocinas.

Kowalewski et al. (2020) relata que "A síndrome da tempestade de citocinas é um estado hiperinflamatório caracterizado por falência de múltiplos órgãos fulminante e elevação dos níveis de citocinas." Este estado de resposta inflamatória exacerbada pode gerar danos pulmonares, cardiocirculatóriose, até mesmo, levar a um choque vasoplégico grave (TOMASZ et. al. 2020). Além disso, o estado hiperinflamatório também pode ser responsável por uma ativação sistêmica das vias de coagulação, o que leva à trombose venosa profunda (TVP) e à coagulação intravascular disseminada (CID). Esta resposta do organismo à infecção resulta em um desequilíbrio entre fatores pró-coagulantes e anticoagulantes (KOWALEWSKI etal. 2020).

IV. Conclusão

A infecção estimula a resposta imunológica complexa nos pacientes, onde os agentes pró e antinflamatórios irão contribuir para eliminar o processo infeccioso e recuperar o tecido. Cada reação imunológica varia de paciente para paciente, pois vários deles possuem fatores determinantes no sistema imunológico. Portanto, há evidências concretas que associam a virulência da COVID-19 a fenômenos de coagulação intravascular que, por sua vez, poderão evoluir à TVP. Além disso, muito embora ainda existam elementos específicos que não foram totalmente elucidados, há grande compreensão fisiopatológica de sua relação a trombos, bem como é uma tendência a inserção de anticoagulantes em seu tratamento.

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Features of the Clinical Course of Urinary Stone Disease in the Farming Population

By Mamasaliev N.S., Abdurakhmonov B.M. & Qurbonova R.R.

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Abstract- In the climatic conditions of the Fergana Valley of Uzbekistan, 2478 people aged 18-70 engaged in farming were studied in a one-time epidemiological study. Questionnaire, clinical, biochemical, instrumental and special urological examination methods were used. The clinical symptoms of urolithiasis are determined to have a number of specific features, including risk factors and comorbidity. Severe urolithiasis and exacerbation of symptoms are observed in patients with a risk factor of 12.8 times, and in the presence of comorbidity - up to 45.7%.

Keywords: farmer population, urolithiasis, clinical course, risk factors, epidemiology, comorbidity.

GJMR-F Classification: DDC Code: 616.622 LCC Code: RC916

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Features of the Clinical Course of Urinary Stone Disease in the Farming Population

Mamasaliev N.S. [α], Abdurakhmonov B.M.[σ] & Qurbonova R.R. [ρ]

Abstract- **In the climatic conditions of the Fergana Valley of Uzbekistan, 2478 people aged 18-70 engaged in farming were studied in a one-time epidemiological study. Questionnaire, clinical, biochemical, instrumental and special urological examination methods were used. The clinical symptoms of urolithiasis are determined to have a number of specific features, including risk factors and comorbidity. Severe urolithiasis and exacerbation of symptoms are observed in patients with a risk factor of 12.8 times, and in the presence of comorbidity - up to 45.7%.**

Keywords: farmer population, urolithiasis, clinical course, risk factors, epidemiology, comorbidity.

I. Introduction

The study of methods of early diagnosis, rates of spread and clinical features of urolithiasis in epidemiological research will help to develop guidelines for the prevention and treatment of the disease in different regions and groups, to reduce disability and mortality, socio-economic losses.

Analysis of available scientific sources confirms these ideas and testifies that this disease is one of the most common diseases [1,2,3].

Another conclusion from the research is that in urolithiasis-related treatment and prophylaxis programs and scientific directions, high-tech-based activities and practices are given more prominence than screening approaches. Based on them, most of the conclusions and recommendations are in the form of "sessile" medical guidelines. In other systemic diseases, it began to develop the opposite, and thus, it was proved that significant and guaranteed positive results could be obtained [4, 5, 6, 7]. It has been proven by many researchers that the foremost effective method in large-scale examinations among the population living in different regions and conditions is to rescue patients from urinary stones and then carry out active prophylaxis [8, 9, 10]. Such scientific and practical activity allows to effectively prevent a large number of complications and recurrent course of urolithiasis [11, 12].

*The aim of the study*was to study and evaluate the clinical features of urinary stone disease in the farming population in the Fergana Valley of Uzbekistan.

II. Research Material and Methods

In the Pakhtaabad climatic zone of the Fergana Valley, 2,478 ≤17-year-olds and ≥18-70-year-old farmers were involved in a one-time epidemiological study and were fully screened. Questionnaire, clinical, biochemical, instrumental and special urological examinations were used in the screening. The questionnaire used was approved by the Ethics Committee of the Ministry of Health of Uzbekistan and approved for use in epidemiological surveys (Kayumov UK, 2020). It provides an opportunity to make a complete epidemiological diagnosis of non-communicable diseases, in particular, urolithiasis and its risk factors (XO).

Ultrasound examinations for the detection of urolithiasis at the prenosological and nosological stages in Toshiba-SAL-32V, ultrasound scanning of urinary tract organs in the SAL-50 ultrasound scanner of the Japanese company "Aloka", 12 connections in ECG mode using electrography "6-NEK", Exo-KG and chest radiography and anthropometric measurements (according to the formula Kettle index = body weight (kg)/height (m^2)).

In the examined population, general analysis of blood and urine, and biochemical parameters were analyzed and studied. Their examination (indicators of total cholesterol, triglycerides, glycemia, uricemia, water-salt and mineral metabolism/blood electrolytes in the blood plasma, indicators of protein metabolism) was carried out using traditional methods widely used in treatment and prevention facilities. Based on international clinical and epidemiological recommendations, urolithiasis risk factors, general urinalysis, and sediment microscopy were studied, evaluated, and used as diagnostic criteria [13].

The following were accepted as the basic diagnostic criteria for urolithiasis or urolithiasis diagnosis was made when they were available [UAE, 2014; Yuldashev F.Yu., 1994]:

- Kidney and urinary tract stones diagnosed by Ultrasound method in the kidneys and upper urinary tract;
- Anamnestic data;
- Renal succulent detection detected by Ultrasound, salt crystals located in the cavities of the pelvic system, and again, salt crystals (SC) found in urine microscopy.

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The farmer population found in SC constituted a risk group.

a) Statistical verification methods

The statistical analysis used Epi Info and Excel 2021 from the Microsoft Office suite. In the study, the effectIn assessing the relationship between the causal factor and the consequence, the risk ratio of biostatistics, a 95% confidence interval to extrapolate the detected risk ratio, was calculated as Xi^2 and R on the Pearson criterion in order to determine the statistical significance of the data obtained. As a result of the single-factor analysis, all influencing factors found to be statistically significant were studied in Mantel-Henszel's multivariate analysis and based on extrapolation. All detected risk ratios and 95% confidence intervals were compared at the logarithmic growth rate in the Forest Plot diagrams.

III. Results and Discussion

Undoubtedly, the study of the regional features of the clinical course of urolithiasis in the farming population in the context of the new Uzbekistan is important. The reason is that such research has not been done at the population level. This topical scientific problem has also been the 'target object' of our study, and we have concluded that the main and specific urological symptoms of urolithiasis have a number of specific features in the farming population. Table 1 and Figure 1 show the prevalence of the main symptoms of urolithiasis in the farming male and female populations.

It turns out that the prevalence of the main symptoms of urolithiasis, with a difference in urolithiasis in male farmers and women, is recorded as follows *(Table-1):*

sudden renal puncture -13.1% and 4.1% ($R_1 > 0.005$; $R_2 < 0.01$),
low back pain - from 70.4% and 57.6% ($R_1 > 0.005$; $R_2 < 0.05$),
severe pain - from 9.2% and 7.0% ($R_1 > 0.005$; $R_2 > 0.05$),
dyspeptic symptoms - from 19.9% and 10.1% ($R_1 > 0.005$; $R_2 < 0.05$),
hematuria - from 11.2% and 8.3% ($R_1 > 0.005$; $R_2 > 0.05$),
dysuria - from 82.3% and 74.9% ($R_1 > 0.005$; $R_2 < 0.05$),
oligoanuria - from 27.4% and 15.8% ($R_1 > 0.005$; $R_2 < 0.05$),
dizziness - from 61.2% and 70.5% ($R_1 < 0.05$; $R_2 < 0.05$),
obmorok - from 40.8% and 36.7% ($R_1 > 0.005$; $R_2 > 0.05$),
bradycardia - from 4.9% and 5.2% ($R_1 < 0.05$; $R_2 > 0.05$) and
increased pain on palpation of the lumbar region - from 54.1% and 41.9% ($R_1 > 0.005$; $R_2 < 0.05$).

Table-1: Epidemiological characterization of the prevalence of the main symptoms of urolithiasis in the farmer population

The main clinical signs of urolithiasis	The farmer is a man			R	Farmers are women			The general population of farmers		
	n	urolithiasis			n	urolithiasis		n	urolithiasis	
		Absolute number	Percentage			Absolute number	Absolute number		Absolute number	Percentage
Acute renal colic	54	412	13.1	> 0.005	16	387	4.1	70	799	8.8
Location of pain in the lumbar region	290	412	70.4	> 0.005	223	387	57.6	513	799	64.2
Extreme pain	38	412	9.2	> 0.005	27	387	7.0	65	799	8.1
Dyspeptic symptoms	82	412	19.9	> 0.005	39	387	10.1	121	799	15.1
Hematuria	46	412	11.2	> 0.005	32	387	8.3	78	799	9.8
Dysuria	339	412	82.3	> 0.005	290	387	74.9	629	799	78.7
Oligoanuria	113	412	27.4	> 0.005	61	387	15.8	174	799	21.8
Dizziness	252	412	61.2	> 0.05	273	387	70.5	525	799	65.7

Obmork	168	412	40.8	> 0.005	142	387	36.7	310	799	38.8
Bradycardia	20	412	4.9	> 0.05	20	387	5.2	40	799	5.0
Increased pain on palpation of the lumbar region	223	412	54.1	> 0.005	162	387	41.9	385	799	48.2

The main symptoms of urolithiasis are divided into three groups according to the frequency of prevalence in the general population of farmers: “symptoms with very high prevalence”, “symptoms with moderate prevalence” and “rare symptoms with reliable differentiation”. The symptoms of the first group include the following, ie they are noted with high frequencies: dysuria - 78.7%, dizziness - 65.7% and the location of pain in the lumbar region - 64.2%. The symptoms of the second group and the percentage of their recording are as follows: increased pain on palpation of the lumbar region - 48.2%, rheumatism - 38.8%, oligoanuria - 21.8% and dyspeptic symptoms - 15.1%. The symptoms of the third group are 4 and are confirmed by the following percentages: bradycardia - 5.0%, hematuria - 9.8%, severe pain - 8.1% and acute renal failure - 8.8%.

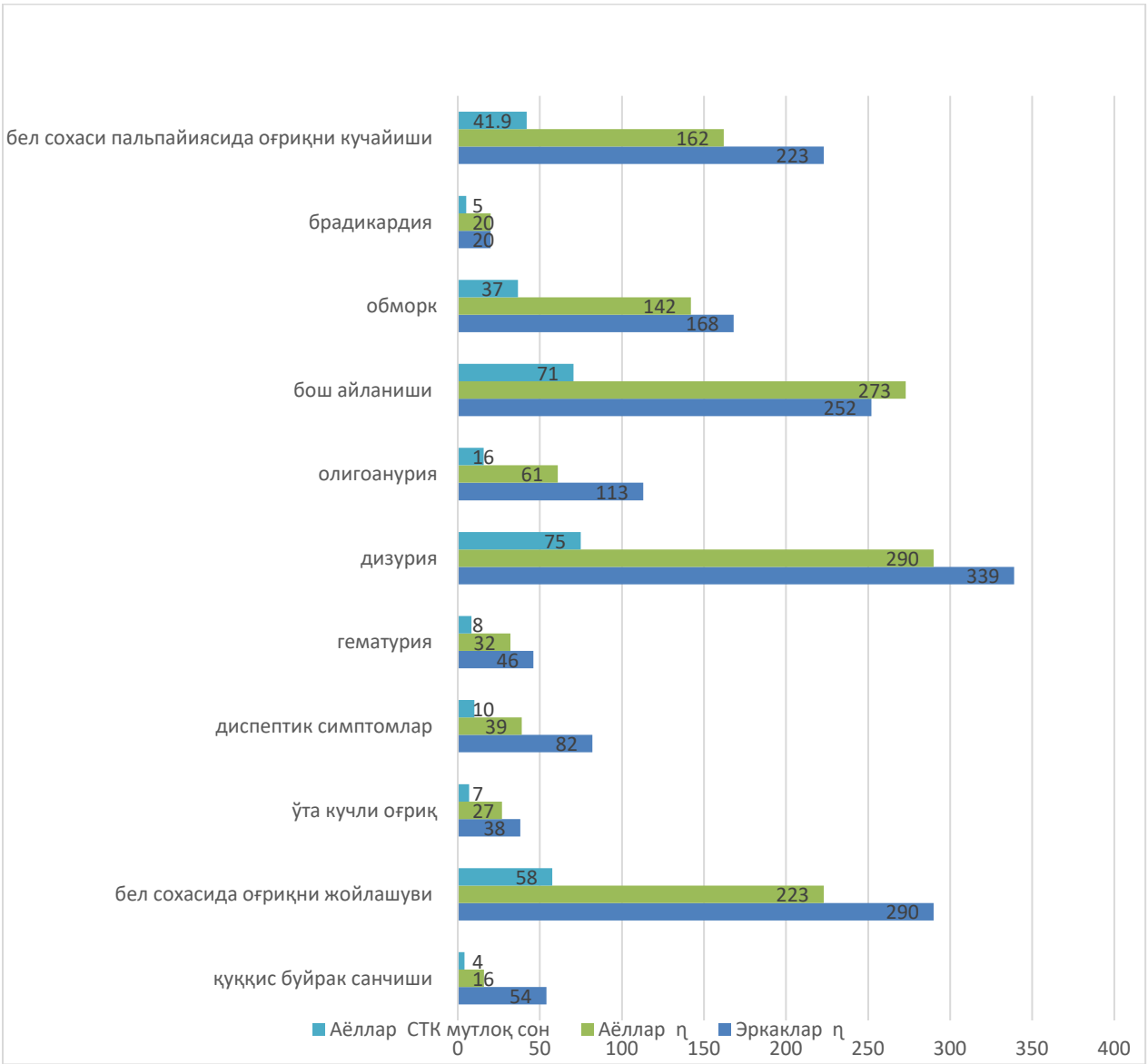

Figure-1: Features of the expression of specific symptoms of urolithiasis in the farming population

Table 2 and Figure 2 describe the epidemiological characterization of the prevalence of major urological symptoms in the farmer population with urolithiasis (STOP) and without urolithiasis (STSP). It follows that in the STOP-male population and in the STSP-male population, the main urological symptoms of urolithiasis are determined by significant differences:

- sudden renal colic - from 13.1% and 1.6% (R <0.05);
- location of pain in the lumbar region - 70.4% and 32.2% (R <0.05);
- severe pain - from 9.2% and 1.2% (R <0.05);
- dyspeptic symptoms - from 19.9% and 2.2% (R <0.05);
- hematuria - from 11.2% and 0.7% (R <0.05);
- dysuria - from 82.3% and 4.3% (R <0.05);
- oligoanuria - from 27.4% and 2.7% (R <0.05);
- dizziness - from 61.2% and 10.0% (R <0.05);
- obmorok - from 40.8% and 4.7% (R <0.05);
- bradycardia - from 4.9% and 2.3% (R <0.05);
- increased pain on palpation of the lumbar region - from 54.1% and 3.5% (R <0.05).

Table-2: Epidemiological characteristics of the prevalence of urological symptoms in the population of farmers with urolithiasis (STOP) and non-STP (STSP)

Basic urological symptoms	STOP male population			R	STS male population			STOP female population			R	STS female population		
	n	urolithiasis			n	urolithiasis		n	urolithiasis			n	urolithiasis	
		Mut-loqson	%			Mut-loqson	%		Absolute number	%			Mut-loqson	%
Acute renal colic	54	412	13.1	<0.05	13	823	1.6	16	387	4.1	<0.05	12	790	1.6
Location of pain in the lumbar region-vi	290	412	70.4	<0.05	265	823	32.2	223	387	57.6	<0.05	254	790	32.2
Extreme pain	38	412	9.2	<0.05	10	823	1,2	27	387	7.0	<0.05	10	790	1,2
Dyspeptic symptoms	82	412	19.9	<0.05	18	823	2.2	39	387	10.1	<0.05	17	790	2.2
Hematuria	46	412	11.2	<0.05	6	823	0.7	32	387	8.3	<0.05	6	790	0.7
Dysuria	339	412	82.3	<0.05	35	823	4.3	290	387	74.9	<0.05	34	790	4.3
Oligo-anuria	113	412	27.4	<0.05	22	823	2.7	61	387	15.8	<0.05	21	790	2.7
Dizziness	252	412	61.2	<0.05	82	823	10.0	273	387	70.5	<0.05	79	790	10.0
Obmork	168	412	40.8	<0.05	39	823	4.7	142	387	36.7	<0.05	37	790	4.7
Bradycardia	20	412	4.9	<0.05	19	823	2.3	20	387	5.2	<0.05	18	790	2.3
Increased pain on palpation of the lumbar region	223	412	54.1	<0.05	29	823	3.5	162	387	41.9	<0.05	28	790	3.5

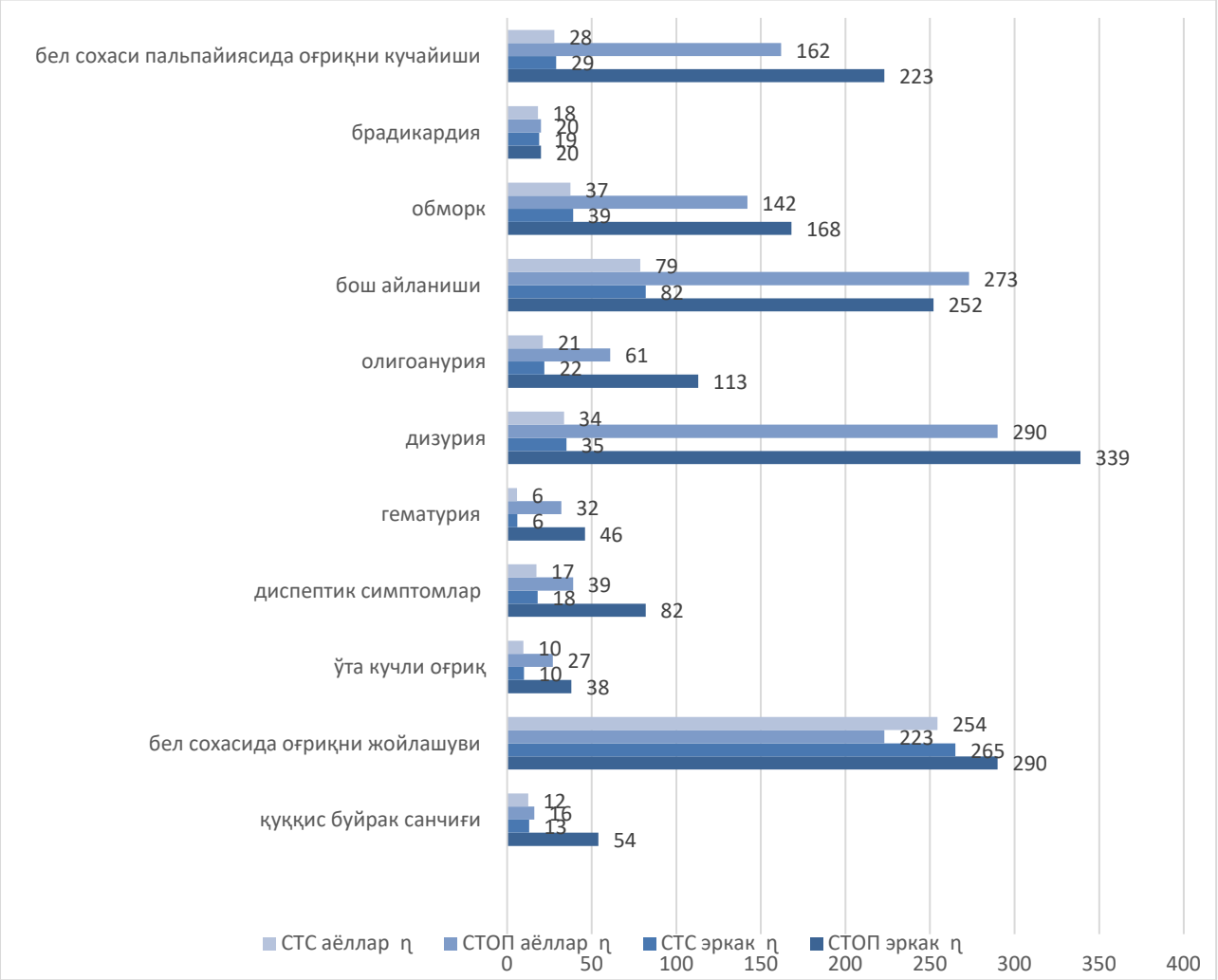

Figure-2: Features of the expression of urological symptoms in the population of patients with urolithiasis (WUL) and non-urolithiasis (NUL).

In our subsequent analyzes, the contributions of the main risk factors to the onset and exacerbation of clinical symptoms of urolithiasis were studied and evaluated (shown in Table 3 and Figure 3).

According to the results of the analysis, against the background of risk factors, the onset and exacerbation of the total symptoms of urolithiasis increases.

Table-3: Comparative description of the main risk factors contributing to the onset and exacerbation of symptoms of urolithiasis in the farmer population

№	Urolithiasis of basic symptoms	Inspection teams (XO available)			R	Inspection teams (no XO)			R
		XO+ urolithiasis (absolute number)	XO total number	Percentage		urolithiasis without risk factors (absolute number)	XO total number	Percentage	
1.	Acute renal colic	70	79	8.7	> 0.005	25	1613	1.5	<0.001
2.	Location of pain in the lumbar region	513	799	64.2	> 0.005	519	1613	32.1	<0.001
3.	Extreme pain	65	799	8.1	> 0.005	20	1613	1,2	<0.001
4.	Dyspeptic symptoms	121	799	15.1	> 0.005	35	1613	2.2	<0.001
5.	Hematuria	78	799	9.7	> 0.005	12	1613	0.7	<0.001
6.	Dysuria	629	799	78.7	> 0.005	69	1613	4.3	<0.001
7.	Oligoanuria	174	799	21.7	> 0.005	43	1613	2.7	<0.001

8.	Dizziness	525	799	65.7	> 0.005	161	1613	9.9	<0.001
9.	Obmorok	310	799	38.7	> 0.005	76	1613	4.7	<0.001
10.	Bradycardia	40	799	5.0	> 0.005	37	1613	2.2	<0.001
11.	Increased pain on palpation of the lumbar region	385	799	48.1	> 0.005	57	1613	3.5	<0.001

For example, in the population examined for the presence and absence of XO, the clinical symptoms of urolithiasis are determined by the following prevalence:

- sudden renal puncture - from 8.7% and 1.5% (R <0.001),
- location of pain in the lumbar region - from 64.2% and 32.1% (R <0.01),
- severe pain - from 8.1% and 1.2% (R <0.001),
- dyspeptic symptoms - from 15.1% and 2.2% (R <0.001),
- hematuria - from 9.7% and 0.7% (R <0.0001),
- dysuria - from 78.7% and 4.3% (R <0.001),
- oligoanuria - from 21.7% and 2.7% (R <0.001),
- dizziness - from 65.7% and 9.9% (R <0.001),
- obmorok - from 38.7% and 4.7% (R <0.001),
- bradycardia - from 5.0% and 2.2% (R <0.01) and
- increased pain on palpation of the lumbar region - from 54.1% and 3.5% (R <0.05).

When there is more than 1 or 2 risk factors in the client population with urolithiasis, its clinical severity increases to 12.8 times. Hence, emergency and planned therapy require that priority be given to both primary and secondary prevention of urolithiasis. Adaptation of risk factor correction to the treatment process, in patients with urolithiasis, is appropriate.

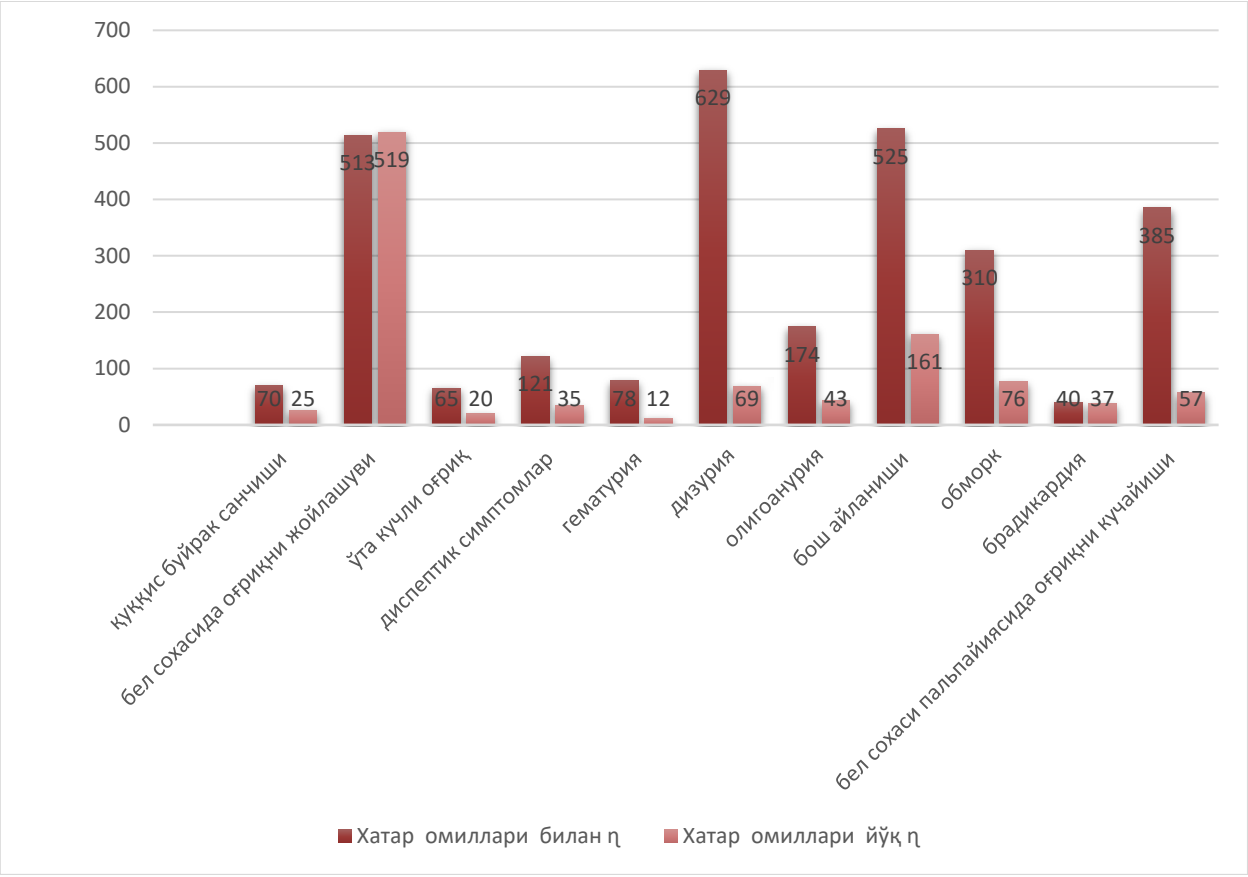

Figure 3: Features of the detection of symptoms of urolithiasis, depending on risk factors

It was also found from our analysis that urolithiasis occurs in most cases on the background of comorbidity (simultaneous involvement of more than two diseases) (our research in this area is numerically described in Figure 3 and Table 4.

Comorbidity ≥is determined by a 45.7 percent prevalence in the general population of 18–70-year-old farmers (Table 4) and exhibits age-dependent formation characteristics. It is noted in different ages with a specific distribution:

- 18-30 years old - 20.0%;
- 31-49 years - 49.9% (with a 2.5-fold increase; R <0.01);
- 50-69 years - 27.9% (with a 1.3-fold increase; R <0.05);
- ≥At the age of 70 - 2.2% (with a decrease of 10 times; R <0.001).

Table-4: Epidemiological characterization of comorbidity in the farming population

Inspection groups	Age groups									
	18-30 years old		31-49 years old		59 69 years old		≥70 years old		≥18-70 years old	
	In the absolute number	Percentage	In the absolute number	Percentage	In the absolute number	Percentage	In the absolute number	Percentage	In the absolute number	Percentage
Farmers are men	38	52.1	98	53.9 IT	74	72.6 x	5	62.5 x	215	58.9
R	<0.005		<0.005		<0.005		<0.005		<0.005	
Farmers are women	35	47.9	84	46.2 IT	28	27.5 x	3	37.5 x	150	41.1
The general population of farmers	73	20.0	182	49.9 xx	102	27.9 x	8	2.2 xxx	365	45.7

Note: • $Xi^2 = 0.05$; • RR = 1.01; • R > 0.05.

With age, comorbidity is detected at different frequencies or observed with a difference. This epidemiologically specific gender view is evident in the following percentage frequencies in male farmers and women:

- 18-30 years - from 52.1% and 47.9% (R <0.005);
- 31-49 years - 53.9 percent (increased by 1.8 percent, R> 0.05) and 46.2 percent (decreased by 1.7 percent, R> 0.05), R <0.005;
- 50-69 years - 72.6 percent (increased by 20.5 percent, R <0.05) and 27.5 percent (decreased by 20.4 percent, R <0.05), R <0.005;
- ≥At the age of 70 - 62.5% (increased to 10.4%, R <0.05); R> 0.005;
- 37.5 percent (with a decrease of 10.4 percent, R <0.05); R> 0.005.

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Cystic Fibrosis- Is it Extremely Rare or Invariably Missed: An Observational Study in Bangladesh Scenario

By M S Khaled, Firoza Akter, Jahangir Khan, Sayedul Islam & Md. Golam Dostogir Harun

National Institute of Diseases of the Chest and Hospital (NIDCH)

Abstract- *Background:* Cystic fibrosis (CF), the most common genetic disorder among the Caucasian population was believed to be extremely rare or non-existent in Indian subcontinent countries like Bangladesh. But the real scenario is not so infrequent as per belief.

Objective: To introduce pilocarpine iontophoresis Sweat Chloride Test (SCT) for the first time in Bangladesh for the diagnosis of CF and to determine the phenotypic spectrum of the disease in Bangladeshi patients.

Methods: A prospective observational study conducted over a period of 3 years including 400 patients (N=400) clinically suspected of CF and pilocarpine iontophoresis sweat chloride tests were performed using locally developed low-cost technology. Sweat chloride estimation was done by Schales and Schales method.

Keywords: *cystic fibrosis, sweat chloride, pilocarpine iontophoresis, bangladesh.*

GJMR-F Classification: *DDC Code: 616.37 LCC Code: RC858.C95*

Strictly as per the compliance and regulations of:

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Results: Among 400 clinically suspected CF patients sweat chloride tests were positive in 38 patients (9.02%). The mean age at diagnosis of CF was 8.92 ± 6.72 years with a male preponderance of 63.2%. The most frequent mode of clinical presentation among study participants was recurrent respiratory tract infection (RRTI). Failure to thrive (FTT), recurrent pneumonia, digital clubbing, nasal polyps, rectal prolapse were statistically significant clinical presentations among SCT positive patients ($p < 0.05$) Bronchiectasis and consolidation in radiology and *P.* aeruginosa and Klebsiella in microbiology were found to be significantly associated with elevated sweat chloride levels. ($p<.05$).

Conclusion: The presence of CF patients in Bangladesh are more common than previous thinking but the diagnosis is often missed or considerably delayed and hence the advancement of the disease. A high index of suspicion among physicians and increasing availability of diagnostic facilities may provide the actual scenario of the disease and enhance the need for the development of country-specific management protocol.

Keywords: cystic fibrosis, sweat chloride, pilocarpine iontophoresis, bangladesh.

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I. Introduction

Cystic fibrosis (CF) is a multisystem genetic disorder that commonly affects children and young adults and is the most common life-limiting disease among the Caucasian population. [1] The disease, although can involve almost all systems of the body, most commonly involves the respiratory and digestive systems with phenotypic presentations of repeated respiratory tract infections, recurrent or persistent pneumonia, malabsorption, steatorrhea and failure to thrive (FTT).

The basic defect in CF is mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene located on the long arm of chromosome 7 at a position of 7q31.2 [2] which results in absence or improper chloride conductance by epithelial cells present on mucosal surfaces leading to dehydration of mucosal secretions that are too thick and viscid and difficult to clear. [3]

Although mutation analysis for CFTR gene might be the confirmatory diagnostic tool, [4] however, because of the large number of mutations, confirmation of CF diagnosis by genetic testing is limited [5] and till today, the mainstay of CF diagnosis is the sweat chloride test. Pilocarpine iontophoresis sweat chloride testing for quantitative analysis of sweat to determine chloride concentration has been the gold standard for the diagnosis of CF for more than a half-century. [6] Indeed, few tests in clinical medicine have the discriminating power of the sweat test. [7]

The incidence of CF is variable in different kinds of literature reported from different corners of the world. The incidence is approximately 1 in 2500 children born in UK [8], less common in African Americans (1: 1500) and Asian Americans (1: 31000) [9]. The accurate incidence of CF among the populations in the Indian subcontinent is exactly not known. CF was thought to be extremely rare or non-existent in this region with a widespread belief that

CF is a disease of white populations, so rarely suspected and diagnosed. But recent review of different published studies, reports and comments indicate that the presence of CF among the people in the Indian sub-continent is much more than previous thinking and the disease is under-diagnosed or missed in the majority of cases. [10]

To our knowledge, till to date, there is no well accepted diagnostic procedure and structured management protocol for CF in Bangladesh.

The present study was designed to introduce the pilocarpine iontophoresis sweat chloride test using an indigenously developed and validated equipment for accurate and inexpensive diagnosis of CF for the first time in Bangladesh and to determine the phenotypic spectrum of CF for raising the physician's awareness about the disease in this country.

II. Materials and Methods

a) Study design and setting

This prospective observational study was conducted over 3 years from January 2017 to December 2019 in the National Institute of Diseases of the Chest and Hospital (NIDCH), the largest respiratory care hospital and academic institute in government level in Bangladesh, in collaboration with Ibn Sine Hospital and Diagnostic Centre, a tertiary level referral Centre in Dhaka, the capital city of Bangladesh. The study was approved by the institutional review board.

b) Study population and sampling procedure

A total of 400 patients suspected of CF- having respiratory and/or GI symptoms, features of FTT, were included in the study regardless of age, sex and socioeconomic status with strictly following the inclusion and exclusion criteria. The majority of these patients were referred from different hospitals and medical centers of the country for proper diagnosis and better management.

A detailed history and thorough clinical examinations were done. Proper investigations for individual patients were advised. All patients or parents provided written consent prior to study commencement and the sweat chloride test was described individually. The clinical features, presence of one or more, considered as criteria to include the patient in the study to undergo sweat chloride test by pilocarpine iontophoresis were – recurrent respiratory tract infections, recurrent/persistent pneumonia, history of CF in siblings, ch malabsorption, steatorrhea, failure to thrive, nasal polyps, rectal prolapse, bronchiectasis in radiology. Patients having clinical and/or laboratory findings suggestive of tuberculosis, bronchial asthma, cong. heart disease, lactose intolerance were excluded from the study.

c) Sweat testing

Sweat chloride tests (SCT) were done by an indigenously developed and validated equipment [11] using low-cost technology. It's a very useful and inexpensive method for sweat collection and chloride estimation in resource poor settings for CF diagnosis (video -1). Sweat collection was done by pilocarpine iontophoresis following Gibson and Cooke method [12] and quantitative chloride estimation in collected sweat, minimum 100 mg collected within 30 minutes, was done by Schales and Schales method [13] and labelled as follows:

The concentration of Chloride (Cl-)	Indicator
< 29 mEq/L	normal
30- 59 mEq/L	borderline
>60 mEq/L	positive [14]

Validation of the SCT results were done periodically by performing chloride estimation on known strength of saline solution. The mean and standard deviation of the difference from the standard was calculated and 95% confidence interval was estimated.

Sweat chloride tests were repeated at least one week apart in cases of positive or borderline results. Patients with normal sweat tests were properly evaluated to come to a diagnosis excluding possible differentials. Patients with borderline sweat test results were treated according to the clinical ground and subsequently prepared for mutation analysis.

d) Statistical analysis

Descriptive analyses were performed using frequency, percentage and mean with standard deviation (SD). Figures in the parenthesis indicate the corresponding percentage. Comparisons were made using the Chi-square test for categorical variables. A p-value of <0.05 was considered as the level of significance. All the statistical analyses were conducted using Stata 16.

e) Ethical consideration

Ethical approval was obtained from the Institutional Review Board (IRB) of both centers (NIDCH/EC/09-2017). Informed written consent and with ascent was taken from each patient or their parents prior to study commencement. Confidentiality and anonymity of the patients were ensured. The sweat chloride test procedure as well as its potential benefit and risks were individually described to the patients and participation was voluntary where the participants had the right to withdraw at any time during the study. In case of refusal/non-response, no discrimination was done. Finally, no financial incentive or compensation was provided to the participants.

III. Results

Out of 400 patients having clinical suspicion of CF and underwent pilocarpine iontophoresis, the test was positive in 38 patients (9.5%) and borderline in 9 patients (2.25%) on two occasions at least one week apart. The

rest of the patients (88.25%) had normal sweat test results (Figure 1).

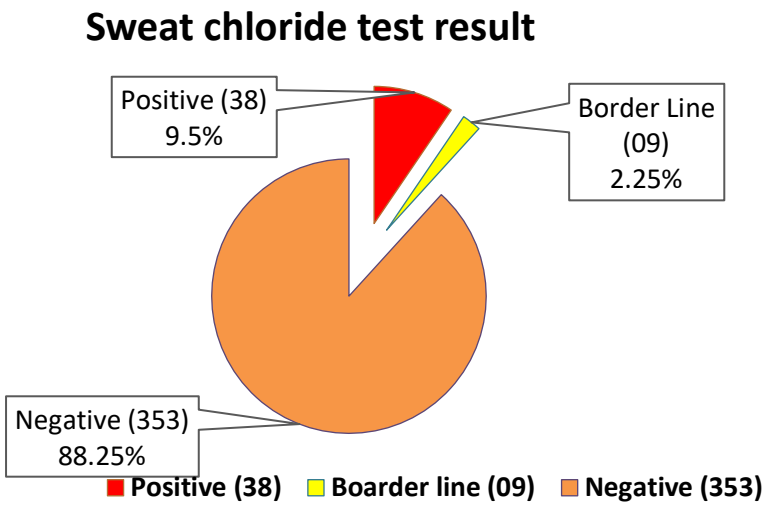

Figure 1: Sweat chloride test result among study population (N=400)

The relationship between the sweat chloride test results of the participants and their socio-demographic characteristics were described in table 1. The mean age of SCT positive patients was 8.92 ± 6.72 years, statistically significant (p<0.05%) number of them were male (63.2%) and reside in rural area (47.4%).

Table-1: Relationship between Sweat Chloride Test Results of the participants and their Socio-Demographic characteristics (N=400)

Characteristics	Positive SCT+Ve (n=38)	Borderline SCT±Ve (n=9)	Negative SCT-Ve (n=353)	P-value
Age group				
<5 years	8(21.1%)	1(11.1%)	85(24.1%)	0.354
5-10 years	20(52.6%)	3(33.3%)	120(34.0%)	
11-15 years	6(15.8%)	3(33.3%)	86(24.4%)	
>15 years	4(10.5%)	2(22.2%)	62(17.6%)	
Mean ± SD, Yrs	8.92 ± 6.72	10.11 ± 5.58	9.21 ± 7.91	0.748
Sex				
Male	24(63.2%)	9(100.0%)	190(53.8%)	0.014
Female	14(36.8%)	0(0.0%)	163(46.2%)	
Consanguinity				
Present	7 (18.42 %)	1(11.1%)	47(13.3%)	0.213
Absent	31 (81.57 %)	8(88.9%)	306(86.7%)	
Residence				
Urban	11(28.9%)	5(55.6%)	168(47.6%)	0.015
Sub urban	7(18.4%)	2(22.2%)	102(28.9%)	
Rural	18(47.4%)	2(22.2%)	83(23.5%)	

Table 2 shows us the relationship between different clinical features of the participants and their SCT results. FTT, digital clubbing, recurrent pneumonia, nasal polyps and rectal prolapse were statistically significant

(p-value < 0.05) clinical presentations in SCT positive patients. On the other hand, persistent pneumonia and hemoptysis were present significantly in borderline SCT patients (p < 0.05).

Table-2: Relationship between different clinical features of the participants and their SCT results (N=400)

Clinical features	Positive SCT+Ve (n= 38)	Borderline SCT±Ve (n= 9)	Negative SCT-Ve (n= 353)	P-value
R R T Infection	33 (86.8%)	6 (66.7%)	297 (84.1%)	0.325
Failure to thrive (FTT)	32 (84.2%)	3 (33.3%)	128 (36.3%)	<0.001
Ch cough with sputum	25 (65.8%)	4 (44.4%)	214 (60.6%)	0.494
Wheezing	23 (60.5%)	5 (55.6%)	205 (58.1%)	0.982
Digital clubbing	17 (44.7%)	1 (11.1%)	53 (15.0%)	<0.001
Recurrent pneumonia	15 (39.5%)	0 (0.0%)	22 (6.2%)	<0.001
Ch Diarrhea	8 (21.1%)	2 (22.2%)	55 (15.6%)	0.608
Persistent pneumonia	4 (10.5%)	4 (44.4%)	28 (7.9%)	0.001
Steatorrhea	5 (13.2%)	0 (0.0%)	26 (7.4%)	0.304
Nasal Polyps	4 (10.5%)	0 (0.0%)	8 (2.3%)	0.016
Hemoptysis	3 (7.9%)	4 (44.4%)	32 (9.1%)	0.002
Rectal prolapse	3 (7.9%)	0 (0.0%)	4 (1.1%)	0.009
Azoospermia	1 (2.6%)	0 (0.0%)	6 (1.7%)	0.845

Table 3 and 4 reflects the relationship between chest x-ray and HRCT findings of the participants and their SCT results. Bronchiectasis and consolidation were the statistically significant radiological findings in SCT positive patients (p< .05).

Table-3: Relationship between chest x-ray findings of the participants and their SCT results (N=340)

Chest X-ray findings	Positive SCT+Ve (n= 38)	Borderline SCT±Ve (n= 9)	Negative SCT-Ve (n= 293)	P-Value
Normal	5 (13.2%)	0 (0.0%)	73 (24.9 %)	0.068
Bronchiectasis	14 (36.9%)	3 (33.3%)	52 (17.7 %)	0.013
Consolidation	12 (31.6%)	1 (11.1%)	47 (16.0 %)	0.008
Prominent broncho Vascular markings	10 (26.3%)	2 (22.2%)	198 (67.6 %)	<0.001
Hyperinflation	8 (21.1%)	2 (22.2%)	190 (64.8 %)	<0.001
Lobar collapse	8 (21.1%)	1 (11.1%)	30 (10.2 %)	0.144
Destroyed lung	4 (10.5%)	1 (11.1%)	22 (7.5 %)	0.761

Table-4: Relationship between HRCT result of the participants and their SCT results (N=201)

HRCT Result	Positive SCT+Ve (n= 38)	Borderline SCT±Ve (n= 9)	Negative SCT-Ve (n= 154)	P-Value
Normal	2 (5.3 %)	0 (0.0 %)	12 (7.8 %)	0.605
Bronchiectasis	26 (68.4 %)	5 (55.6 %)	52 (33.8 %)	<0.001
Consolidation	18 (47.4 %)	1 (11.1 %)	40 (26.0 %)	0.016
Consolidation/collapse	0 (0.0 %)	1 (11.1 %)	30 (19.5 %)	0.011
Air trapping/Mucus plugging	8 (21.1 %)	2 (22.2 %)	18 (11.7 %)	0.250
Cavity	8 (21.1 %)	2 (22.2 %)	46 (29.9 %)	0.515

The microbiological profile shown in table 5 reveals that Pseudomonas and Klebsiella were found to have highly statistically significant prevalence in the specimens of SCT positive result holders than other groups (p = 0.001).

Table 5: Relationship between the microbiological profile of the participants and their SCT results (N=320)

Microbiological Profile	Positive SCT+Ve (n= 38)	Borderline SCT±Ve (n= 9)	Negative SCT-Ve (n= 273)	P-Value
No growth	0 (0.0 %)	2 (22.22 %)	55 (20.14 %)	0.009
Pseudomonas	22 (57.89 %)	2 (22.22 %)	60 (21.97 %)	<0.001
Streptococcus	7 (18.42 %)	2 (22.22 %)	112 (41.02 %)	0.017
Staphylococcus	9 (23.68 %)	4 (44.44 %)	118 (43.22 %)	0.070
H. Influenza	4 (10.52 %)	3 (33.33 %)	98 (35.89 %)	0.008
Klebsiella	17 (44.73 %)	0 (0.0 %)	55 (21.14 %)	0.001
Moraxella	0 (0.0 %)	0 (0.0 %)	25 (9.15 %)	0.096
Acinetobacter	1 (2.63 %)	1 (11.11 %)	19 (6.95 %)	0.513
Aspergillus	1 (2.63 %)	0 (0.0 %)	08 (2.93 %)	0.869

IV. Discussion

Cystic Fibrosis (CF), considered to be the most common genetic disorder among the Caucasian population had remained largely unrecognized in developing countries like Bangladesh. Clinical features of this disease individually resemble those of other common diseases in this country like asthma, pneumonia, tuberculosis, chronic diarrhea etc. and the diagnosis may be missed invariably and patients treated wrongly with frequent changing physicians (video-2). Due to low index of suspicion, physicians usually not consider CF in a differential diagnosis. On the other hand, due to unavailability of pilocarpine iontophoresis SCT in Bangladesh, physicians have to rely on patient's clinical presentations for making a diagnosis and treating the patient. In a few centers, sweat collection is done for analysis by an indigenously wrapped sweating technique[15] where to whole body of the patient is wrapped with a long piece of polythene and heat generated by room heater for sweating which is not well established and validated rather hazardous often for pediatric patients and also inconsistency in sweat chloride results. Moreover, alternate procedures are no longer acceptable for the diagnosis of CF [16]. The present study has introduced an indigenously developed inexpensive technology for the diagnosis of CF by quantitative pilocarpine iontophoresis sweat chloride test

and also brought to light the phenotypic spectrum of CF in this country.

In the present study, sweat chloride test was conducted in 400 patients with high clinical suspicion and diagnosis of CF was based on the CF Foundation guidelines in consensus report in 2008 for diagnosis of CF i.e., presence of characteristic clinical features of CF or history CF in a sibling or a positive newborn screening test result plus a positive sweat chloride test or presence of two CF causing mutations or abnormal nasal potential differences. [17]

Among 400 patients included in the study, the sweat chloride test was positive in 38 patients (9.5%). In India, Kabra et al. [18] conducted a study in the All-India Institute of Medical Sciences (AIIMS) pediatric chest clinic and found sweat test was positive in 3.5% of patients which is lower than our study. Another study conducted in India by Manzoor A. Raina et al. [19] found sweat chloride test positive in 22.5% of patients which is much higher than the present study. These differences might be due to differences in the number of study population, age at presentation of disease symptoms and variation in geographical and ethnic populations. No such study has been conducted previously in this country and further studies are needed to get the actual scenario of CF in Bangladesh.

The mean age at diagnosis of CF in our study was 8.92 ± 6.72 yrs with a range of 2 – 32 yrs which is close to the studies reported by Homash et.al [9] and Kawoosa et al. [20] where the age at diagnosis was 9.6 yrs and 10.5 yrs respectively. The age at diagnosis of CF is much higher in the Indian sub-continent [21] in contrast to the patients of USA where 71% of CF cases are diagnosed by 1st year of life. [22] Reality might be due to low index of suspicion among the treating physicians and lack of proper diagnostic facilities.

Regarding gender discrimination, there was a male preponderance of the disease in SCT positive patients in our study (63 % male vs 37% female) which is statistically significant ($p < .05$). This could be related to greater attention received by the male child and greater provision of medical care to them.

Consanguinity was present in 18.42% of SCT positive patients in present study, not significant statistically ($p > 0.05$) but this finding is supported by a study in India [18] where 19.2% of CF patients were presented with consanguinity. However, a higher rate of consanguinity was reported in CF patients in studies reported from Middle East countries. [23,24]

Statistically significant number of CF patients (18, 47.4%) in present study were from rural area and 29 % and 18 % patients from urban and sub urban areas respectively ($p < .05$). This might reflect the aforementioned thoughts about CF being a rare disease and also financial constraints and long travels to get sweat test done.

The most frequent mode of clinical presentation among the study participants was repeated respiratory tract infection. FTT, digital clubbing, recurrent pneumonia, nasal polyps and rectal prolapse were the significant clinical manifestations among SCT positive patients ($p < .05$). On the other hand, persistent pneumonia and hemoptysis were present significantly in borderline SCT group. These clinical manifestations are almost similar to the studies reported by Raina et al. from India [19], El Falaki et al. [25] from Egypt and Farahmand et al. [26] from Iran with few differences in percentages in some points of clinical involvement which might be due to differences at the age of CF diagnosis and also big differences in study samples.

Failure to thrive (FTT) was present in 84.21 % of the SCT positive patients in present study, highly significant statistically ($p < .001$). Shaha et al. [27] reported FTT in 83.9 % and Kabra et al. [18] reported in 90 % of CF patients in their studies, which supports the present study.

Clinical presentations of pancreatic insufficiency such as ch. Diarrhea, steatorrhea was present in 28.94 % and 18.42 % of patients respectively in SCT positive group, not significant statistically in present study. Raina et al. [19] from India reported diarrhea in 31.7 % and steatorrhea in 85.3 % of patients in their study. El – Falaki et al. [25] from Egypt reported steatorrhea in 66.7 % of CF patients which is much higher than the present study. Pancreatic insufficiency might be less in Bangladeshi population than others due to different genetic variants could be a speculation for this reason and could be a matter of thinking for future researchers in their next studies.

Regarding radiological profile, bronchiectasis and consolidation were the significant radiological findings in both X -ray and HRCT of the chest in SCT positive patients ($p < .05$). Almost similar radiological findings were shown by Aziz DA et al. from Pakistan and Kawoosa et al. from India. [28,20]The presence of bronchiectasis, an end-stage pulmonary disease in the majority of CF patients at the time of diagnosis indicates the delay in diagnosis and advancement of the disease deterioration.

The microbiological profile obtained from sputum and throat swab culture revealed the preponderance of P.aeruginosa (57.89 %) and Klebsiella (44.73 %) in SCT positive patients and highly significant statistically ($p = .001$). This finding was supported by Indika et al. from Srilanka (60 %) and Shah et al. from Pakistan (87 %).[29,27] Bowler et al. in their study found the growth of this pathogen at a significantly earlier age in Asian patients and may adversely affect the outcome. [30] It was not possible for us to sub type the P. aeruginosa into mucoid or non-mucoid strains. A more accurate pattern of lung infection would emerge from bronchoalveolar lavage (BAL) fluid study after bronchoscopy.

The strength of this study is that, this is the first study in Bangladesh introducing the SCT by quantitative pilocarpine iontophoresis, the gold standard for the diagnosis of CF, using an indigenously developed and validated low-cost equipment instead of performing sweat chloride test by wrapping the whole body and heating for collection of sweat which is obsolete and too risky for young patients. However, the study has some limitations. Only 38 cases could be diagnosed over 3 years and lack of adequate follow-up services and therapeutic modalities.

V. Conclusion

Cystic fibrosis does occur in the Bangladeshi population far more than anticipation and in the majority of cases, the diagnosis is delayed and at that time the disease is far advanced.

A stronger and more structured system is required for proper diagnosis and effective management of this disease. Creating awareness among the physicians about the disease along with adequate training regarding proper sweat collection and chloride estimation in any suspected CF patient is necessary. Also need to develop a management protocol for CF patients based on locally available recourses.

Authors contributions:

MSK= Conceptualized the study design, collected data and wrote the initial manuscript.

FA- Helped in data collection, Microbiology laboratory tasks and revision of manuscript.

JK- Helped in data collection and Biochemistry laboratory work.

SI- Analyzed and interpreted the data. Critically analyzed the manuscript.

MGDH– Statistical analysis and revision of the manuscript.

All authors read and approved the final manuscript.

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Ethics approval and consent to participate: The study was approved by the IRB (NIDCH/EC/09-2017) and written consent was taken from each patient and/or parent.

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We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

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Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

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2. Drafting the paper and revising it critically regarding important academic content.
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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

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11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

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- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

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Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

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An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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	A-B	**C-D**	**E-F**
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Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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