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This is Not What I Want, Doctor

By Keerti Saxena & Patricia D'Urso, D'Urso
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Abstract- A qualitative transcendental phenomenological study was conducted to explore the lived experiences of the physicians who may perceive their professional integrity challenged by and in conflict with patient autonomy and patient consumerism. A sample of fifteen physicians was drawn from a population of physicians practicing medicine in the central Tennessee area for the last 5 years or more. Open ended one-on-one interview questions revealed a rich data on personal lived experience that was analyzed using Modified van Kaam approach by Moustakas. A subjective interpretation of the data identified an emergence of five main themes. Those themes were (1) autonomy of patients must be acknowledged, (2) consumeristic behavior of patients in healthcare market was increasing, (3) physicians' roles are evolving in response to demands of consumerist patients, (4) physicians expressed dissatisfaction with burdens associated with evolving roles, and (5) increased burdens have created conflicts in physician-patient relationship.

Keywords: revolutionized healthcare delivery, patient autonomy, patient consumerism, professional integrity, participatory relationship.

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This is Not What I Want, Doctor

Keerti Saxena [α] & Patricia D'Urso, D'Urso [σ]

Abstract- A qualitative transcendental phenomenological study was conducted to explore the lived experiences of the physicians who may perceive their professional integrity challenged by and in conflict with patient autonomy and patient consumerism. A sample of fifteen physicians was drawn from a population of physicians practicing medicine in the central Tennessee area for the last 5 years or more. Open ended one-on-one interview questions revealed a rich data on personal lived experience that was analyzed using Modified van Kaam approach by Moustakas. A subjective interpretation of the data identified an emergence of five main themes. Those themes were (1) autonomy of patients must be acknowledged, (2) consumeristic behavior of patients in healthcare market was increasing, (3) physicians' roles are evolving in response to demands of consumerist patients, (4) physicians expressed dissatisfaction with burdens associated with evolving roles, and (5) increased burdens have created conflicts in physician-patient relationship. There is a struggle to find a balance between the information-driven patients' right to autonomy and the physicians' obligations to fulfill their professional duties of providing the best possible patient care, while ensuring that the healthcare resources are being utilized efficiently and fairly. There was a gap in the understanding of the patient-physician relationship in context to the newer era of healthcare. The findings of this research study addressed the gap by providing new information to reevaluate the perception of physician-patient conflicts.

Keywords: revolutionized healthcare delivery, patient autonomy, patient consumerism, professional integrity, participatory relationship.

I. Introduction

The physician-patient relationship is the foundation of the medical practice of healing and at the core of medical ethics (13,32). In the past few decades, this relationship has evolved from the paternalistic physicians and silent patients of Hippocratic era to the empowered and autonomous patients of the current era (32). Numerous factors have contributed to the evolution of physician-patient relationship and in reshaping the quality and structure of healthcare delivery. Healthcare is rapidly being transformed by new medical technologies and empowered, computer-informed patients (5, 29). The information that physicians gather during treatment of their patients and the treatment decisions they make are no longer theirs. The information is protected health information (PHI). The legislative healthcare reforms have also contributed to revolutionizing healthcare and redefining physician-patient relationships (21). Information technology, comprising of an array of medical equipment and mass media, has become the tool of revolutionized healthcare delivery of the 21st century (35). The healthcare revolution is transforming the physician-patient relationship from the classic physician paternalism model to the modern patient autonomy model, one in which the patients are increasingly taking ownership of their health and health-related decision making (5). Patient consumerism and patient autonomy are now new dimensions to the physician-patient relationship and together, a force to be reckoned with.

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II. A Research Study - Purpose, Problem, and Method

The purpose of the qualitative transcendental phenomenological study was to explore the lived experiences of the physicians who may perceive their professional integrity challenged by and in conflict with patient autonomy and patient consumerism. In this qualitative phenomenological study, the lived experiences were elicited through in-depth, face-to-face interviews. A phenomenological design was appropriate for the research study because it provides a rich and meaningful description of lived experience in a balanced way (25). The phenomenological design of the research study embodied rich descriptions of lived experiences of a phenomenon (11). The use of phenomenological design ensured focus on the wholeness of the experience and permitted the sharing of subjective perception of the phenomenon experienced by the physician. Knowledge gained through transcendental approach has the potential to contribute to resolution of problems and overall productivity (4). In the qualitative research study, transcendental phenomenological method was beneficial in uncovering the deeper meaning and understanding of the challenges by, and conflicts with, patient autonomy and patient consumerism and perhaps found a resolution of participatory relationship between the physicians and patients.

The general problem addressed in this qualitative study was the impact of increased patient autonomy and patient consumerism on healthcare delivery. The specific problem addressed in this qualitative phenomenological study was the conflicts and challenges posed to the physicians' professional

integrity due to increased patient autonomy and patient consumerism.

A sample of 15 physicians was drawn from a population of physicians practicing medicine in the central Tennessee area for the last 5 years or more (from the date of research study). Two open-ended research questions and 10 interview questions revealed rich data on the personal-lived experiences of the physicians residing and practicing in the central Tennessee area.

III. "I want This and not That, Doctor!"- Patient Consumerism

The provider-patient relationship is a privileged one but also a complex one (6). Several factors have influenced the dynamics of physician-patient relationships and the way physicians deliver healthcare services. One such important factor was patient consumerism. A consumerist patient seeks sources other than the physicians to acquire medical information and rely heavily on such information (9). Patient consumerism is on the rise. Internet has quickly become the alternative and most popular source of healthcare information. There is a vast amount of healthcare information available through Internet. Web-sites like WebMD (2014) and Health line (2014) instantly provide vast information on the diseases, diagnosis, medical explanations, and possible treatments. According to the statistics released by The Pew Research Center, approximately 59% of the American adults have retrieved health information online, 35% have looked online for specific medical conditions, approximately 33% of cell phone owners have used their cell phones to access health information, and 19% of smart-phone owners have downloaded health applications (12). The easily accessible information on the Internet has increased people's knowledge, a sense of ownership of one's health, and the awareness of patient's rights and autonomy.

Another factor influencing physician-patient relationship was the advertising and marketing of healthcare services directly to the patients. The healthcare technology has transformed patients into healthcare consumers, who in turn influence the services provided in the market (26). Patients are considered consumers and healthcare services are considered a product. Patients are the main target population in the marketing and advertising of healthcare services and products. Medical Direct-to-Consumer advertising or DTC advertising has affected the physician-patient relationship (10). Purchasing many of advertised healthcare products require a physician's approval and prescription first, but that has not deterred the advertising trend of these medical and healthcare products. Some of the surveyed physicians reported that they are pressured by the patients to prescribe the DTC medications. The physicians expressed concerns that the drug companies advertise various benefits of such DTC medications without context, while not fully disclosing the risks and side-effects.

Patients are using the newly acquired knowledge based on multiple web-based sources and television advertisements to customize their care. Armed with such knowledge, many patients walk into their doctors' offices with their own 'lists' of 'wants' and 'don't wants'. They are very specific about requesting certain medications and/or procedures and rejecting certain medications and/or treatment plans. All they appear to be looking for is a validation of their requests in the form of a certified physician's signature.

IV. "This is not What I want, Doctor!" - Patient Anatomy

The revolutionized healthcare delivery has the possibility of unintended adverse impacts on physician-patient relationships, while creating political, social, and ethical challenges (30, 31). Enforcement of HIPAA laws and the new Patient's Bill of Rights resulted in an increased awareness of patients' rights and ownership of one's health. Patients are considered autonomous individuals with the right to seek, alter, and reject medical treatments. New medical technologies, Internet access, and multiple health-related websites on the Internet are newer venues, apart from the physicians, to obtain information about health. Internet access has become a cornucopia of medical information.

However, the responding physicians pointed out that if the information on the Internet is inaccurate, irrelevant, and misinterpreted, then Internet-acquired information often leads to inappropriate requests by patients for clinical interventions, challenging physicians' authority, miscommunication, and damaging to physician-patient relationship (22). Increased patient autonomy and patient consumerism have led to discordant expectations between physicians and patients (3). Patients often exercise autonomy and consumerism to reject treatments prescribed by their physicians or to demand treatments that may be against medical advice. The refusal of or demand for treatments leads to discordant expectations. Discordant expectations create uncertainties regarding the physicians' roles and authorities (3). They also lead to a loss of trust by the patients in their physicians' beneficence and their clinical judgments.

V. The Physician-Patient Conflicts

In the early 1900s, physicians established themselves as the ultimate and knowledgeable healthcare professionals who knew what was best for their patients (14). In the process, patients were

categorized as the ailing and the vulnerable population who sought the physician's expert advice to become better. The unquestionable authority of the physicians and the dependence of the patients on such authority led to an accepted paternalistic approach to medical care. Within this approach, the physician was in control while the patient was under the control.

From the Hippocratic era of physicians' paternalism to the Affordable Health Care Reforms era of patient autonomy, the physician-patient relationships have evolved drastically, as the decision-making has shifted from the paternalistic physician to the autonomous patient (32). After conducting an extensive literature review, a gap emerged on the subject of understanding the evolving of patient-physician relationship in context to the newer era of healthcare. It pointed to the challenges physicians face relative to their professional integrity and obligations resulting from increasing patient autonomy and patient consumerism.

Internet based information and direct-to-patient advertising are the new cultural and social forces that perceive the patients as the consumers of healthcare products and services. The consumerist patients are obtaining clinical knowledge through media and Internet sources, outside direct consultations with their physicians (2). Empowered by the exclusive attention by advertisers and new-found knowledge through the Internet and television, it appears that patients are more willing to challenge their physicians' clinical authority.

A tension is created between a patient's autonomy and a physician's clinical duties, when a patient is in disagreement with the physician's plan of care. According to Lantos, Matlock, and Wendler (2011), this tension poses the dilemma of how the physicians should approach cases in which their own medical integrity is challenged by and in conflict with the need to respect a patient's autonomy (p. 495). Patient consumerism and patient autonomy, when misinformed and misdirected, often lead to physician-patient conflicts.

Increasing patient autonomy and patient consumerism appeared to pose increasing challenges to physicians' professional integrity. A physician-patient consultation could turn into a conflict due to lack of information, lack of support, perception of indecisiveness, and challenge to personal values (20). When the consumerist patient demands customized health care that a physician believes is not conducive to good health care, a conflict arises between the patient's autonomy and physician's clinical decision making. Dealing with conflicts with patient autonomy is a challenge to a physician's own integrity, which in turn evokes anger and frustration among physicians (15). Conflicts in a physician-patient relationship lead to ineffective medical outcomes. Conflicts compromise the clinical integrity as well as the health care outcome.

Entwistle, Carter, Cribb, and McCaffery (2010) emphasized the value of patient autonomy but raised questions regarding its overemphasis. Entwistle et al. (2010) contended that the autonomy of patients should be respected as an important aspect of biomedical ethics. However, respecting patient autonomy does not mean that the patients should dictate their health care while the physicians stand by and honor the patients' wishes. It also does not imply that physicians should not discuss or question a patient's choices, while allowing the patients to take any course of action related to healthcare. It also creates a less than optimal medical outcome that negates the purpose of consulting an expert physician. The acceptance of reduced professional responsibility or an uninvolved physician is even worse. A dire need to set certain boundaries to the usage of autonomy is necessary to avoid abuse of individual responsibilities (16).

Preventable medical errors were another manifestation of outcomes that create conflicts. According to a study done by the Institute of Medicine, preventable medical errors are responsible for more than 98,000 deaths per year, incurring healthcare expenses of approximately $29 billion (1). Clash of interests or power struggle between the patients exercising their autonomy and physicians striving for optimal outcomes created negativity and deviation from the goal of superior patient care. These disagreements cause poor judgments that lead to harmful, yet preventable, medical errors.

The physicians also have an ever-present fear of lawsuits (33). The fear of lawsuits from the patients provokes the physicians to trust their patients less and practice defensive medicine. Simultaneously, the suspicions of being over-tested by the physicians makes the patients trust their doctors less. A lack of mutual trust mars the relationship between patients and physicians leading to malpractice litigations. The tedious, expensive, and slow litigation process can be emotionally draining and damaging to the reputation of the physicians (7).

VI. The Committed Physician

A deeper analysis of the responses to the one-on-one interview questions of the research study led to an unexpected outcome of the research findings. The unexpected outcome was that the physicians believed that there are no apparent direct conflicts between the physicians' professional integrity and patient autonomy. On the contrary, the physicians welcomed their evolving roles as an educator, a guide, a counselor, a coach, and a partner. Another frequently emerging sentiment of the interviewed doctors was that they viewed themselves as an advocate to their autonomous and information-seeking patients. All participating physicians used these terms at one point or the other, seeming to

take pride and enjoying being a guiding counselor while imparting their own valuable knowledge. Additionally, all participating physicians referred to the patients as 'my patients' rather than 'those patients', at one point or the other during the interviews.

The conflicts arose when the physician beneficence or the desire to do good was mired in some of the external factors. Those external factors were a) Controlling, time-consuming, and costly mandates by the government and insurance companies, b) Lack of proper resources and sufficient compensations to implement such mandates, c) Lack of control in the physicians' decision-making authority, d) Misguided concepts of patient autonomy and patient consumerism, and e) A lack of support from some of the medical organizations.

These findings indicated a sense of dissatisfaction among the participating physicians towards their changing responsibilities. The physicians are feeling burned out by the imposing and controlling factors that have seeped into the direct physician-patient relationship. They are frustrated by the diminishing control over their medical decision-making. They are also feeling excessively burdened by the increasing time-consuming mandates with no backup of proper resources and compensations.

However, in spite of the frustrations, the physicians continued to strongly believe in the sanctity of physician-patient relationship and their profession. They felt that their medical knowledge and long years of training gave them a unique opportunity to contribute to their patients' quality of life. The participating physicians viewed themselves as the advocates and partners of their patients, more so, during the evolving healthcare environment.

VII. Significance of the Study

The significance of this phenomenological transcendental study was that the study's results contributed to a better understanding of the underlying reasons of conflicts between the physicians' professional integrity and patient autonomy in context to patient consumerism. Exploring the underlying problems helped physicians ascertain the impact of conflicts and thus make better decisions (27). By understanding the reasons for conflicts, efforts can be made to strategically overcome those reasons and establish a positive and participatory relationship between physicians and patients.

Another related significance of this qualitative study was that the results may contribute to assuring effective, efficient, equitable, and timely delivery of healthcare, even as new healthcare reforms are rapidly changing the roles of physicians and patients. In order to meet the demands of changing roles, there is a need to move away from the old model of physician paternalism to patient-centered care and partnership (18). The transformation of physician-patient relationship to partnership and team-care may facilitate the mitigation of potential litigations and promote patient and physician satisfactions.

An important significance of the research study was to encourage leadership among the physicians. Their clinical judgment, their clinical and empirical knowledge, and their clinical skills are valuable in contributing to meeting or exceeding the standards of patient care. Practitioners must take the lead in risk management and safety delivery. To be leaders in healthcare organizations, licensed healthcare practitioners must possess the qualities of integrity, compassion, courage, and emotional maturity (28). The significance of the healthcare leadership lies in facilitating the establishment of a participatory professional relationship between patients and their physicians to promote a better overall health outcomes and functionality (17, 24).

The findings may expand the emphasis from the broader issue of general conflicts in physician-patient relationship to the focused issue of physician dissatisfaction due to controlling and interfering external factors that may be contributing to the physician-patient conflicts. Contribution to the knowledge may result in reevaluating the physician-patient relationship in the era of empowered patients and healthcare reforms, thereby finding more appropriate ways to improve physician satisfaction.

The study will also be significant to the stakeholders of the healthcare system, who may use the findings for making decisions regarding efficient healthcare delivery. Some of the crucial stakeholders of the healthcare system are the physicians and their staff, the patients, the hospitals and their administrators, the government, the policymakers, the pharmaceutical companies, the insurance companies, the medical organizations, the medical suppliers, and the healthcare leaders.

VIII. Concluding Discussion

In this research study, an attempt was made to examine how the physicians perceive the autonomy of patients as a challenge to clinical decision-making process. The goal of the study goal was to uncover deeper meaning and understanding of the challenges by, and conflicts with, patient autonomy and consumerism, as perceived by the participating physicians. The immediate revelation of the study was that the physicians are feeling burdened, frustrated, and burned out. The surprising revelation of this study was that they do not blame the consumerist and autonomous patients who are demanding customized patient-care. The surveyed physicians expressed confidence in customizing their healthcare delivery,

while maintaining the highest professional integrity of a physician. They had confidence in their knowledge, training, experience, and above all, their rapport with their patients. They took pride in being the advocate and counselor to their patients in the trying times of rapidly evolving healthcare landscape.

Collectively, the surveyed physicians voiced an immense dissatisfaction with the controlling, time-consuming, costly and often unnecessary mandates by the government and insurance companies. Compounded with the lack of proper support and adequate resources, and sufficient compensations to implement the mandates, the evolving healthcare era had inadvertently led to the loss of control in the qualified physicians' decision-making authority and dissatisfaction.

To overcome some of the dissatisfactions, a physician may opt to becoming a hospital employee. Hospitals are aggressively seeking physicians to hire them as employees for the hospitals' motives of gaining market share and increasing patient volume (23). Becoming a hospital-employed physician may not resolve the crucial concerns of the physicians regarding the loss of their professional decision-making authority. It may only serve to eliminate the burdens of practicing private medicine with the increasing operating costs and increasing responsibilities. A certain amount of physician-satisfaction may be derived by shifting such burdens to the hospitals, in exchange for a stabilized salary, stabilized work-hours, and a work-life balance.

If they choose to remain self-employed, physicians may opt to practice concierge medicine. Under the concierge medicine or direct-pay model, the physicians eliminate insurance billings altogether and collect a flat fee for their services, directly from the patients (34). Eliminating insurance billing facilitates returning of the clinical decision-making authority to the physicians, customizing their fee according to the paying abilities of their patients, and freeing the physicians from the obligations of several intrusive and unnecessary insurance mandates. As noted by Weiczner (2013), there are more than 5,500 concierge medical practices in nation, reporting that concierge model has enabled them to reduce overhead costs by 40%, while reducing patient-fee. It is anticipated that under an established standard of accountability and transparency, the concierge medicine model will provide the physicians the satisfaction of providing quality care to the best of their abilities, without impinging upon their professional integrity. The physicians practicing concierge medicine may overcome their collective frustrations over the issues of loss of authority, time-constraints, burdens of mandates, and reimbursement-reductions. The professional satisfaction may lead to physicians perceiving patient autonomy and patient consumerism as participatory and not adversary outcomes of the healthcare reforms.

The research findings have contributed to the body of knowledge by drawing attention to the mandatory healthcare reforms that failed to take into consideration some of the adverse impacts on the physicians, the patients, and the healthcare industry. The physicians' job satisfaction and a participatory physician-patient relationship are essential in enhancing the quality of patient care. It is anticipated that the subjects, the organizations, and the society will benefit from the enhanced physician-patient relationships that may lead to mitigating risks, lowering healthcare costs, and improving the overall quality of the healthcare delivery.

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Clinical Governance for Improving Quality of Healthcare

By Bachchu Kailash Kaini

Introduction- Different groups of healthcare professionals work together, and they are an integral part of the health and social care system. They are subject to regulation, compliance, national and local policies, guidance, protocols and accountability arrangements for patient safety, clinical effectiveness, and improved service users' experience. Quality is the heart of the health services, and quality in regards to clinical governance is defined in three broad strands – 'patient safety, clinical effectiveness and patient experience' (Department of Health, 2008, p.47).

Clinical governance is a continuous process for improving and sustaining quality of care delivered to service users. Clinical governance ensures clinical quality is placed at the heart of the health services, and healthcare professionals for the delivery of the highest standards of care by reducing failures, and shared learning.

All service users in health and social care settings expect to receive quality healthcare. Quality in healthcare is not a new concept and it goes back to conceptualization of health and medical science. All healthcare organizations, healthcare professionals, service providers, service users, and stakeholders involved in the delivery of healthcare understand the importance of providing the best care possible to all service users. One of the important objectives of healthcare providers is to ensure that they offer better care through the reduction or errors and waste, and the delivery of effective patient care.

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I. Introduction

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High-quality care means safe and effective care with positive service users' experience (National Quality Board, 2011). Healthcare organizations are responsible for the quality of care they deliver to service users. It is the responsibility of healthcare professionals to recognize their roles in providing high-quality care, and sharing good practice (Leathard, 1994).

Quality healthcare is dependent on various factors such as the provision of healthcare services, allocation of resources, training opportunities to healthcare professionals, culture, skills, and competency of healthcare professionals, supervision and monitoring of care etc. Healthcare organizations, governmental authorities, healthcare professionals, and all stakeholders have to take responsibility for the delivery of quality healthcare and should be accountable for the care they provide.

II. Clinical Governance

Clinical governance is everyone's business, and it is not an optional provision to healthcare professionals and organizations. In essence, every healthcare organization should have a proper system and structures for clinical governance at all levels.

The NHS Scotland, 2007 has defined clinical governance as a mechanism through which 'health services are held accountable for the safety, quality and effectiveness of clinical care delivered to patients'. This has been described as an 'umbrella term' by the Royal College of Nursing (2013) to deliver high standard of care, to continuously improve the health services, and to maintain high standard of care and experience.

Clinical governance promotes a learning culture, and develops a system to deal with and learn from errors, mistakes, incidents, claims, complaints, and to identify and manage risk in healthcare organizations. It links national standards with the local protocol and guidance, and defines an external and internal system of accountability for healthcare professionals and organizations.

According to Winter (1999), clinical governance is 'a systematic approach to assure the delivery of high-quality health services with the active participation of clinicians and patients supported by managers'. Winter highlights the involvement of clinicians, and the support of healthcare managers to make them accountable for ensuring and meeting the standards of patient care. The definitions above justify that healthcare professionals need to work together to deliver safe and high-quality health services. The Clinical Royal College of Nursing (RCN, 2013) states that 'governance aims to improve the quality of care through strengthening

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existing systems, delivering evidence-based practice and encouraging a training and development culture' (p.5).

III. Clinical Governance Framework

The ultimate aim of clinical governance is to deliver high-quality of care by promoting safety, open, and no blame culture. Communication, leadership, patient involvement, and high-quality data are the foundation of healthcare governance; whereas clinical effectiveness, risk management, patient focus, the interface between services, professional self-regulation, continuous professional development, and research and developments are the pillars of clinical governance. Clinical governance is seen as a mechanism and framework for improving the quality of health services.

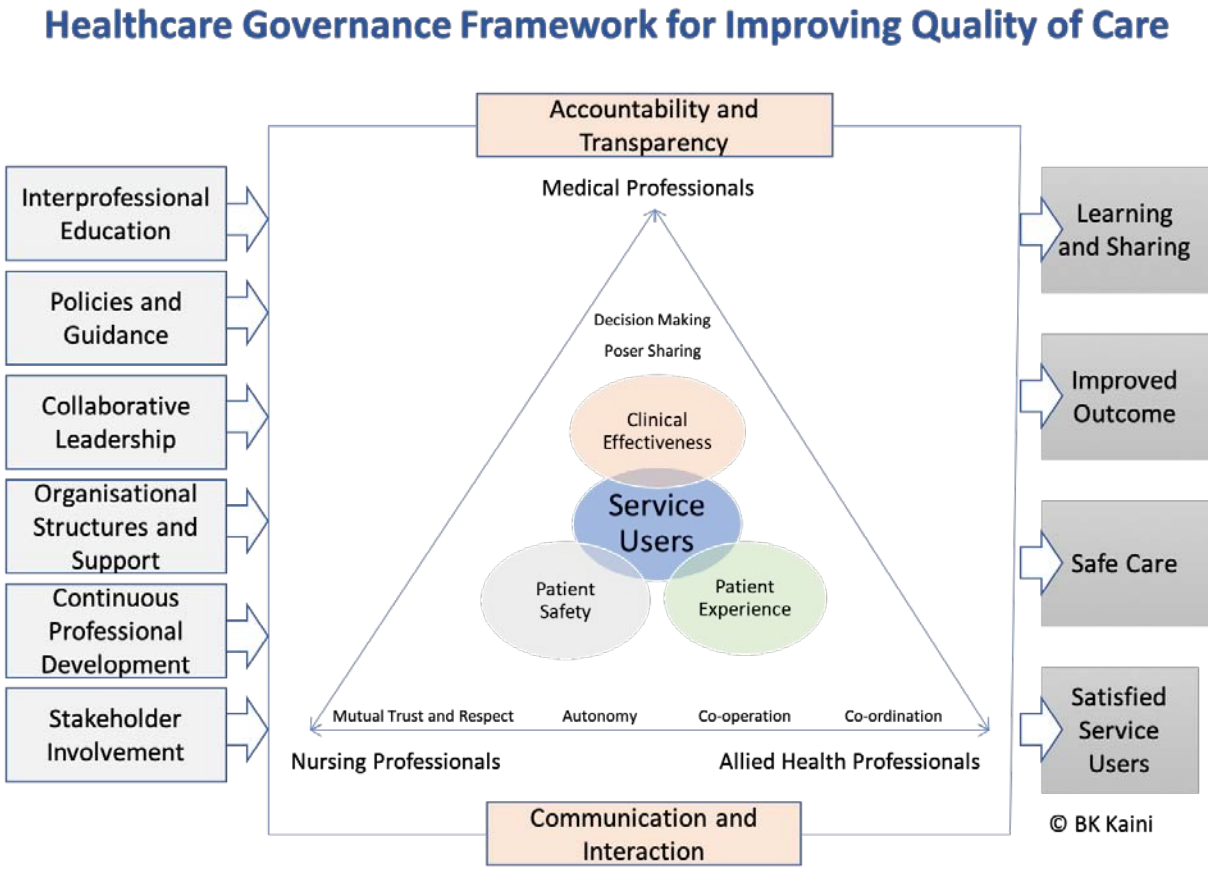

Figure 1: Clinical Governance Framework and Interprofessional Working Environment for Improving Quality of Care

The clinical governance model focuses on the utilization of resources, leadership, open communication, and teamwork for patient safety, clinical satisfaction and patient experience through shared learning and strategic approach. Walshe (2000) highlights the importance of leadership in clinical governance, and asserts that transformational leadership is an appropriate choice for the implementation of clinical governance agenda in healthcare organizations.

The implementation of clinical governance agenda is very important alongside developing strategies and policies. Clinical governance model, policies and plans remain on paper without a proper system of implementing them for the benefits of healthcare professionals, organizations, and service users. The Royal College of Nursing (RCN, 2013) states that supportive culture, equity and consistency of services, quality at the centre, and partnership in care are the main four principles of the implementation of clinical governance agenda in healthcare organizations. Department of Health (1999d) has outlined the following principles for implementing the clinical governance agenda:

- Establish leadership, accountability and working arrangements;
- Carry out a baseline assessment of capacity and capability;
- Formulate and agree on a development plan in the light of this assessment;
- Clarify reporting arrangements for clinical governance within Board and Annual reports.

(Department of Health, 1999)

Patient safety is of great importance to healthcare service users, and it cannot be compromised at any cost. Clinical effectiveness is measured in terms of effectiveness of services provided to service users. Clinical audit measures clinical practices against the national and local standards. Healthcare professionals play vital roles in the implementation of interprofessional working and clinical governance agendas for many reasons. It can be concluded that the clinical governance framework ensures that health services are patient-centerd, and focuses on achieving the highest possible care delivered to service users.

The concept and model of clinical governance in healthcare settings and organizations improves quality of care, service users and staff satisfaction, and team performance. Successful interprofessional working practices in healthcare settings contribute for improving quality of health service delivery. Improved quality of care, better staff satisfaction, improved team performance and better communication and interaction are the benefits of implementing the clinical governance framework in healthcare organizations and settings.

a) Transparency and Accountability

Transparency and accountability are the two pillars of clinical governance (Scally and Donaldson, 1998; Bloor and Maynard, 1998). Openness ensures that healthcare professionals develop a culture of sharing information and knowledge; and learning from mistakes in their clinical practices in healthcare organizations. The true openness includes the sharing of practice and experience that 'went wrong', with the intention of learning on how to improve the services, and not to repeat the same mistakes in the future.

A clear line of responsibility and accountability for the safe, effective and efficient delivery of healthcare is required at all levels. The lack of accountability in the health services is one of the contributory factors for the failure of effective and efficient health services (Kaini, 2013). The clinical governance process ensures that the service providers are liable, responsible and answerable to tax payers, service users, and all stakeholders.

Healthcare is one of the biggest industries, and shared learning is vital to deliver an efficient health service to service users. Through the shared learning process, healthcare professionals learn from each other, and discover about themselves and other colleagues (Milburn and Walker, 2009). Health service delivery is an interactive process and requires coherent and aligned efforts to continuously review the roles and responsibilities of healthcare professionals.

b) Collaborative Leadership

Collaborative leadership is one of the major contributing factors for successful interprofessional working in hospitals (Chong et al., 2013). Similarly, successful implementation of clinical governance within the health services depends on the leaders who are able to inspire and motivate other professionals (Swage, 2005). The role of leadership in interprofessional working is performed usually by the participants to drive the interprofessional working agenda forward, and the leaders of interprofessional working team are guided by policies, protocols, guidance, and standards. Stonehouse (2013) asserts that the implementation of clinical governance agenda requires positive and strong leaders at every level. In this context, healthcare leaders should be able to drive both clinical governance and interprofessional working agendas together for the safe and effective clinical care.

Maximizing nurse-physician collaboration holds promise for improving patient care and creating satisfying work roles (Lindeke & Sieckert, 2005).

c) Interprofessional Working

Clinical governance is about the delivery of high-quality care which is not achievable without teamwork and collaborative practices (Hallett and Thompson, 2001). The successful development and implementation of interprofessional care in healthcare organizations are dependent on, but not restricted to, many professionals, people and organizations such as healthcare regulatory bodies, healthcare professional organizations, academic institutions, hospitals, community and support agencies, healthcare staff and professionals, researchers, service users, government, health caregivers, educators, and administrators (HFO, 2010).

The main aim of all these stakeholders is to deliver effective healthcare, and to satisfy service users without doing any harm to them through interprofessional collaborative practices. Therefore, interprofessional working is directly linked with clinical governance in terms of improving quality of care, patient safety, clinical effectiveness and service users' satisfaction. Clinical governance plays a vital role in improving patients' experiences, decreasing disparities in healthcare and shared learning from the experiences by promoting openness, and culture of accountability (Kaini, 2013).High-quality of care leads to professional pride, and it focuses on improving health services by energizing and motivating all healthcare professionals, and staff (Department of Health, 2008).

If healthcare team fail to deliver, the quality of care deteriorates and it has direct impact on the care of service users (Stonehouse, 2011). The benefits of interprofessional working such as improved standard of patient care, patient safety, and improved patient outcomes are widely cited in the literature (Yeager, 2005). Other benefits such as increased patient satisfaction, preventing fragmentation of care by introducing and applying holistic approach to care are

also cited by research scholars (Haward et al., 2003; Vazirani et al., 2005; Atwal and Caldwell, 2005). Interprofessional working is essential for the survival of healthcare organization (Petri, 2010). Similarly, the importance of clinical governance for a healthy healthcare organization, for safe patient care, and satisfied service users is highlighted by Swage (2005).

Literature confirm that there is a direct correlation between successful interprofessional working, and quantifiable service improvements in patient safety and quality of delivery of health services (The Joint Commission, 2002; Institute of Medicine, 2001). In order to improve the quality of health services, healthcare professionals are required to follow an interprofessional working approach. A single healthcare professional or groups or professionals working in an un-coordinated way cannot achieve the aim of effective delivery of health services.

d) Better Communication, Co-ordination and Interaction

Communication is 'an integral ingredient for the success or failure of healthcare governance' (McSherry and Pearce, 2011, p.143). Different authors and research scholars have mentioned various reasons why communication plays a vital role in healthcare governance; such as it helps to communicate goals, purposes and outcomes (Evans, 1994); shares important and useful information (D'Amour et al., 1999); supports the negotiation between different groups of healthcare professionals (Mariano, 1989); and helps to build mutual respect and trust (Hemmeman et al., 1995).

Various research have shown that poor communication and relationships among and between healthcare professionals can be harmful to service users and result in increased rates of clinical incidents and errors (Larson, 1999; Espin & Lingard 2001, Lingard et al., 2002; The Joint Commission, 2002; Manser, 2009). Lack of communication and co-ordination between healthcare professionals is seen to be a potentially serious factor in compromising good care.

Communication to service users and among healthcare professionals refers to aspects of openness, style, and expression of feelings and thoughts (Interprofessional Education Collaborative, 2011). Service users and healthcare professionals can influence each other in the process. Quality of interaction and communication among healthcare professionals, and between service users may also influence the decision-making process. Hornby and Atkins (2000) assert that the relationship of a healthcare professional with the service user is also based on training and experience, and the balance of power is more on the side of healthcare professional.

Interaction, open listening and communication are collaborative skills required for healthcare professionals (Norman, 1985) to implement clinical governance agenda for the successful delivery of healthcare (McSherry and Pearce, 2011). Open communication is all about passing appropriate information without any barriers and defensive methods that can be easily understood and assimilated by service users. Open communication promotes transparency and patient safety in health service delivery, and helps to improve quality of care.

e) Education and Training

Educational experiences and the socialisation process that occur during the training of each health professional reinforce the common values, problem-solving approaches, and language/jargon of each profession (Hall, 2005). According to Pype et al. (2013), knowing each other's expertise is not sufficient, but need to have role-specific competencies. Interprofessional education, practice and research can have economic benefits and effective clinical outcomes, which may be viable means for improving healthcare delivery (Paul and Peterson, 2002).

According to Firth-Cozens (1999) risk management, change management, team dynamics, clinical audit, professional development and training are the major areas for development in terms of developing competencies required for healthcare professionals in implementing clinical governance agendas.

f) Continuous Professional Development

Continuous professional development, regular review and reflection of clinical practices are important components of clinical governance (White, 2015). One of the important aspects of clinical governance is learning from complaints and adverse incidents (Stonehouse, 2013). Continuous professional and skill development for healthcare professionals in areas such as communication, change management, teamwork and leadership is important to the successful operation of interprofessional care team (ECIP, 2005, pp.5). Strong support from management, adequate resources and appropriate structures for the healthcare team and clinical care are required for improving quality of care, patient safety, and patient experience. Furthermore, different healthcare professionals have different capacities and different capabilities for different healthcare settings based on their skills, competencies, familiarities, and comfort levels. Mu et al. (2004) argue that many healthcare professionals do not have adequate understanding of other colleagues' roles due to a lack of adequate training and education in interprofessional skills. They further assert that healthcare professionals tend to preserve a traditional role concept and territoriality concerns due to lack of adequate training, skills and knowledge.

Team cannot succeed unless its members are able to contribute three types of skills and experiences:

problem-solving and decision-making skills, technical or functional expertise, and interpersonal skills (Natale et al., 1998). Interpersonal and communication skills are fundamental skills for interprofessional working (Minore and Boone, 2002). The lack of communication skills is one of the major contributing factors of patient safety incidents in healthcare (Joint Commission, 2002).

g) Involvement of Service Users

Service users are at the heart of interprofessional care and collaborative practices (University of British Columbia, 2008) and quality improvement process (Department of Health, 2008; Stonehouse, 2013). The existence of healthcare professionals is for service users. Healthcare professionals need to engage, involve and listen to service users and act upon the comments, feedback and experiences of their service users to deliver, and improve health services. Partnership approach that empowers and optimises human resources is one of the potential solutions to meet service users' expectation in healthcare with limited resources (McWilliam et al., 2007).

Lord Darzi's report *High Quality Care for All* (Department of Health, 2008) highlighted that service users' experience is one of the key components of high-quality of care.

Service user involvement is an opportunity for individuals to play an active role in clinical decision-making process for their treatment and care, and for involving in debate about planning decisions for local organizations, and the delivery of health services. Engel and Gursky (2003) assert that service users benefit from inclusion as members of the service delivery team, and they need to be assured that their personal circumstances, feelings and preferences are acknowledged and acted upon.

Healthcare professionals are responsible for updating with the recent developments and learning skills for improving safe and effective clinical care (Stonehouse, 2013). Interprofessional care empowers healthcare professionals (Canadian Medical Association and the Canadian Nurses Association, 2006), and empowered professionals improve the quality of care and patient safety (Department of Health, 2008).

h) Organizational and Clinical Policies, Protocols and Guidance

Organizational and clinical policies, protocols and guidance are the best means of ensuring clinical effectiveness, which is an important component of clinical governance (White, 2015). It ensures that everything healthcare professionals do is meant to provide the best outcomes for service users by adopting an evidence based approach and doing the right thing to the right person at the right time, and in the right place (National Quality Board, 2011). Policies and protocols for clinical governance are important elements that support improving quality of care. Local, national and organizational policies and clinical protocols are required for the safe delivery of health services.

i) Organizational Structures and Support

An organizational framework including structures and systems for clinical governance at organizational and team levels is required to make improvements as envisioned by clinical governance framework (Lugon and Seeker-Walker, 1999). Organizational structures directly and indirectly influence interprofessional care and team outcomes (Pina et al., 2008; Odegard, 2005; Glasby and Dicknson, 2008) and teams cannot function without a clearly defined organizational and team structure (Baxter, 2007). Department of Health (1998) describes a clinical governance model that sets standards to make sound clinical judgments, and to work effectively alongside with clinical judgments for high-quality health services and patient care.

j) Regulation and Compliance in Healthcare

A regulatory body in healthcare is an autonomous (by the introduction of an Act/regulation) and professional body that should be responsible for licensing healthcare organizations, assessing healthcare services, and monitoring the quality of care healthcare provided by healthcare organizations and professionals. The main objective of a regulatory body is to protect, promote and maintain the health and safety of the public by ensuring proper standards in the healthcare practice. The regulatory bodies through the legislation develop system and process for maintaining, improving and sustaining quality of care in healthcare organizations.

Regulatory bodies are established to exercise regulatory functions such as imposing requirements, restrictions and conditions, setting standards in relation to any activity, and securing compliance or enforcement (Total Professions, 2019).

The increasing number of private healthcare providers in the recent years around the globe has also proved an urgent need for regulating healthcare providers in a structured way, and to focus on harmonizing work towards the standards of private, non-governmental, and public healthcare services. Quality regulation may focus more on the assurance of safety than on improvement of wider performance, but this will depend on how the market develops. According to the King's Fund (2005), to formulate an appropriate regulatory response will require significant monitoring, and sharing of intelligence. This will require better co-ordination and co-operation between various regulatory bodies in healthcare such as professional councils and regulatory bodies.

IV. Conclusion

In summary, clinical governance is a framework for improving quality of care, and access by increasing accountability and promoting transparency for the excellent outcome of healthcare, shared learning and sharing. The concept of clinical governance and improving quality of care are inseparable from the health services, and both concepts complement to each other for the safe and effective delivery of healthcare by working together.

As discussed above, the clinical governance model for improving quality of care summarises the relationships between clinical governance and improving quality of care. It also highlights the importance of interprofessional education, training and learning for improving quality of care.

The scope and principles of clinical governance and improving quality of care go beyond simply meeting the expectation of service users and healthcare professionals. Various healthcare professionals, disciplines, roles and organizations are involved in the process of clinical governance and improving quality of care. Healthcare professionals are skilled and trained in their clinical fields, and they work together with other professionals, service users and families to share their knowledge, skills and expertise, and serve the service users. In terms of healthcare governance, the scope of healthcare professionals work is very wide, and it includes developing appropriate structures, policies and guidance, agreeing on approaches to enhance skills, and sharing knowledge for patient safety, clinical effectiveness and patient experience.

Leaders and management should ensure that they take forward clinical governance as a framework for improving quality of care. Moreover, healthcare organizations need to provide adequate resources in terms of funding, training, education, time and structures. The following points summarise how the introduction of the principles and practices of clinical governance helps to improve quality of care in healthcare institutions and settings:

- Promotion of openness, transparency and accountability.
- Collaborative leadership.
- Interprofessional working.
- Better communication, co-ordination and interaction.
- Education and training.
- Continuous professional development.
- Involvement of service users.
- Organizational and clinical policies, protocols and guidance.
- Appropriate organizational structures and support.
- Provision of regulation and compliance

The demand for healthcare professionalsis ever increasing in a rapid pace due to various reasons such as population growth, complexities in health and social care, rise in long term conditions, and the growing number of elderly people. New ways of clinical practices are emerging in light of the development of new technologies, and the emergence of new specialties and sub-specialties. Therefore, introducing the concept and framework of clinical governance and developing culture, system and process for clinical governance certainly help to improve quality of care, patient safety and service users' experience in healthcare organisations and settings.

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Critical Care Air Transport in Northern India: A Retrospective Analysis

By M N Vijai, P R Ravi & Abhishek Patania

Introduction- Critical care medicine has developed and progressed by leaps and bounds in the recent past which resulted in better outcomes of critical patients.(1) Military operations along with natural or manmade disasters are two scenarios where critical patients are left in austere environment or the environment is made austere. Providing advanced life support facilities in the austere environment may not prove to be economical or sustainable, hence the need arose for mobile ICU or the CCATT (Critical Care Air Transport Team) for immediate and faster transport of critical patients to advanced ICU centers. Firstly, by doing this the critical patient is not denied the best available post resuscitation care and secondly the burden on medical resources at the periphery is reduced and they can concentrate on managing the less critical patients. Military medical concept of 'stay and stabilize' over the time, changed to 'scoop and scoot' with 'in transit stabilization'. Aero medical transport has its own challenges and constraints.(2) This requires proper planning and prior training of the CCATT. Although protocols are not formulated, endeavour is to integrate initial resuscitation of critical causalities at the peripheral medical set up with optimal post resuscitation care at advanced ICUs. CCATTs are tasked to simultaneously manage multiple high-severity casualties, and each team is trained to manage multisystem trauma, burns, shock, respiratory failure, and other serious illnesses and injuries.

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Critical Care Air Transport in Northern India: A Retrospective Analysis

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I. Introduction

Critical care medicine has developed and progressed by leaps and bounds in the recent past which resulted in better outcomes of critical patients.(1) Military operations along with natural or manmade disasters are two scenarios where critical patients are left in austere environment or the environment is made austere. Providing advanced life support facilities in the austere environment may not prove to be economical or sustainable, hence the need arose for mobile ICU or the CCATT (Critical Care Air Transport Team) for immediate and faster transport of critical patients to advanced ICU centers. Firstly, by doing this the critical patient is not denied the best available post resuscitation care and secondly the burden on medical resources at the periphery is reduced and they can concentrate on managing the less critical patients. Military medical concept of 'stay and stabilize' over the time, changed to 'scoop and scoot' with 'in transit stabilization'. Aero medical transport has its own challenges and constraints.(2) This requires proper planning and prior training of the CCATT. Although protocols are not formulated, endeavour is to integrate initial resuscitation of critical causalities at the peripheral medical set up with optimal post resuscitation care at advanced ICUs. CCATTs are tasked to simultaneously manage multiple high-severity casualties, and each team is trained to manage multisystem trauma, burns, shock, respiratory failure, and other serious illnesses and injuries. CCATTs are a high-demand, low-density resource, designed for utilization within a full spectrum of operations, including disaster response, small-scale contingencies, homeland security, and war.

The concept of CCATT was first started in the US air Force and the CCATT in US consists of three persons including one physician specializing in critical care, pulmonology, or surgery, a critical care nurse and a respiratory technician. (3,4) In the Indian Air Force, CCAT team and its PTU developed a bit later and consists of an anesthetist and four operating room assistants trained in critical care and emergency procedures.(5)PTU is self-sustainable in terms of power and oxygen supplies for about 3.5 hours. This suits Indian conditions as the flying time is not more than 3 hours duration. For evacuation and transport of longer duration, suitable aircrafts having the facility for onboard charging of electro medical equipment and oxygen facility are utilized. Military aircrafts generally used are both fixed wing and rotary aircrafts based on the place from where medical evacuation has to be carried out. In the recent past, CCATT have been set up in North Eastern and Northern parts of India and evacuations are being carried out from areas in peace, counter insurgency areas and natural disasters like floods and earthquakes.

Limited studies exist regarding the epidemiology of patients transported by CCATTs internationally and almost nil in the Indian scenario. This study is intended to gain insight on the kind of critical patients encountered specially in a high altitude stressful physical environment (in northern India) which can prove to be helpful in deployment of suitable manpower and also in training of the CCAT team. Further we will discuss experiences and lessons learnt from CCAT missions.

II. Methods

This is a report of all the air evacuations done in the northern region of India from Dec 2015 to Dec 2016. During this period, a CCAT team was always at standby at Air Force Station; Hindan and CCAT missions were undertaken when required. Details of all the transfers were maintained in a standardized format. The current paper presents a descriptive analysis of these CCAT missions. Data was entered and analyzed using Microsoft Excel 2017.

III. Results

A total of 53 persons were evacuated/ transferred by air between Dec 2015 and Dec2016 with Air Force Station, Hindan (Ghaziabad) as its Nodal Centre. All the transfers were undertaken by missions dedicated for transfer of patients only.

Out of the tri-services, most transfers were for the Indian Army, 92.5% (49/53) and 7.5% (4/53) for the Indian Air Force personnel.

Just two (3.8%) transfers were for the dependents of serving personnel while 51 (96.2%) transfers were of the serving personnel.

The age of patients evacuated ranged from 20 years to 57 years old. Mean age of the people transferred was 35.7 years with a standard deviation of

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8.9. Median age was 35.0 years and 35.0 years was the mode too. Thus, it was a fairly normal distribution.

The flight time of missions ranged from 30 minutes to 210 minutes. The mean duration of flight time was 82.8 minutes with a standard deviation of 37.2. Thirty out of 53 transfers took 75 to 105 minutes.

Fixed wing aircrafts were used for all missions, while in one mission a helicopter was used too.

Transfers due to battle injuries were 14 (22.6%), whereas 41(77.4%) of the transfers were due to diseases/emergencies of non-battle origin.

Looking at the causes of transfers, 58.5% were from causes which can be classified as surgical, while 41.5% were by medical causes.

Table 1: Provisional diagnosis/cause leading to immediate transfer

Sr. No.	Type of disease	Frequency
1.	Cerebrovascular accident, CNS pathology	9
2.	Burns	6
3.	Abdominal Disease (UGI bleed, Ac. Pancreatitis, abdominal tumours, hepatic failure abdominal trauma)	8
4.	Respiratory Pathology	5
5.	Cardiac Event	5
6.	Gunshot/ Splinter injuries	12
7.	Snake bite	2
8.	Trauma to extremities (# femur, spine, head injury)	4
9.	Hypothermia	1
10.	Cellulitis/Sepsis	1

As seen in table 1, gunshot or splinter injuries were the most common cause leading to immediate transfer. Three gunshot injuries were in chest and abdomen each, one involved both chest and abdomen, two lead to fracture of femur, one was in neck and one in the head.

In flight interventions like intubation, anesthetic or analgesic medications, vasopressors were used in 42 (79.2%) of the transfers. A secure IV line was maintained before flight in all evacuations and around 80% patients were transferred with infusion of normal saline or ringers lactate.

Analgesic medications were used in 47.2% patients.

Oxygen either by a mask or endotracheal tube was administered in 60.5% of patients.

Around one fourth of the transfers were done along with a ventilator support.

Table 2: In flight interventions done in patients transferred by CCAT team

Sr. No.	On board Intervention	No. of patients administered
1.	Ionotropic support	8
2.	Anaesthetic drugs	6
3.	Urinary catheterization	2
4.	Intubation	1
5.	Bag and mask ventilation	1
6.	Amiodarone	1
7.	Pressure bandage	1
8.	Morphine	1

Patients were given priority for air evacuation based on severity of illness and requirement of air evacuation with priority 1 requiring immediate transfer to an intensive care facility. (5) One third of the patients transferred were in Priority 1. Around half of the patients were in Priority 2, while the rest one sixth were in Priority 3.

There were a few complications during some missions but there was no onboard death in any of the air evacuations. The complications sometimes encountered were bleeding from nose, broad complex tachycardia, delay due to bad weather.

Follow up data of 40 patients could be obtained. Thirty two (80%) of these patients recovered and were discharged or transferred back. One fifth of the patients died in the hospital.

IV. Discussion

CCATT in IAF took off in the year 2007 in the North Eastern region with Jorhat (Assam) as the nodal centre from where CCAT missions were managed. Subsequently, CCAT teams were also formulated at Hindon (near Delhi), since the last 2 years, to cater to the needs of the units in the Northern region of India. At Hindon, CCAT missions gained momentum and 53 evacuations of critical patients were undertaken from areas in peace, mostly due to very harsh environmental conditions and in anti-terror operations hostilities during a period of one year. The problems of the northern sector are different than the north eastern sector in terms of both environmental stresses as well as enemy hostilities. Most of the air evacuations in North India were for the Indian Army mostly from high altitude or areas where counter insurgency operations are undergoing. In these parts, air evacuations not only save life or limb, but also play a vital role in boosting the morale of the troops. If we look at the demography of patients, most of them are serving soldiers in the productive years of life. Around three fourths of the transfers are due to non-battle reasons, showing the importance of CCAT even in the times of peace.

The reason for transport of a patient can give us information about the requirement of equipment and training needs of member of CCATT. Our results show

that traumatic injuries lead to around half of all air evacuations undertaken in North India and out of these the most frequent morbidity were gunshot wounds. This can be compared to the report by Mason et al (6) in the year 2006 on 133 patients transported from Balad Air Base, Iraq, over a period of on year. They also reported trauma to be the most common factor among patients undergoing air evacuation, but most common finding was burns as compared to gunshot wounds in the present observation. Medical causes like cardiovascular and respiratory diseases and hypothermia constituted about two-fifths of the patient transfers, which highlight the importance of availability of drugs, oxygen and ventilator support for the patients in the transport aircraft. Around one fourth of the patients transferred, were on ventilator emphasizing the training of CCAT team members in critical care and emergency procedures like endotracheal intubation and resuscitation. The average travel time seen in our study shows that the CCAT teams should be prepared to work in the closed environment of aircraft for around two hours, which may extend in some special cases. The two main restrictions faced in the aircraft are that of lack of space and aircraft noise that makes it difficult to pass instructions. Therefore, each member has to know his role and should be familiar to the working environment in an aircraft. In around 80 percent of the patients, some intervention had to be made. Mostly medicines or anesthesia drugs needed to be administered. A good practice therefore, done in all the patients was ensuring a secure IV before the transfer of patient to the aircraft.

In 2009, Bridges and Evers(7) performed the largest retrospective epidemiologic analysis of CCATT patients to date, reporting on 1,418 patients from Operation Iraqi Freedom/ Operation Enduring Freedom. This analysis revealed a high prevalence of traumatic brain injuries, soft tissue trauma, and burns. Because of this analysis, several troop surges have occurred, and mortality and morbidity rates have changed. The epidemiology reported in these studies suggests different injury patterns compared to previous wars. This is likely due to the changing nature of contemporary warfare, but may also be because of sampling during different stages in an ongoing armed conflict.

We can conclude that transport of critically ill patients has been successfully carried out in the Indian Air Force, but it is still in the developing phase and many possibilities are yet to be explored. The use of aero medical evacuations in the civil set up in India is almost negligible in India and can use experiences gained by the Indian Air Force. Although CCAT have not been deployed in disaster relief in India, there is a scope of application of CCAT teams in civil disasters and a model for this was described by Sariego J. (8)

This is the first analysis of its kind in India and therefore can act as a stepping stone for future research and evolution of CCAT in India. As it is a retrospective analysis, it lacked planning and collection of information actively. The information obtained was limited and a planned, goal oriented study is proposed with due consideration for follow-up of patients. Another limitation is the sample size, which was beyond the control of investigators for such type of analyses, but it has to be kept in mind that these missions are not so common and getting a big sample size will prolong the duration of observation. These studies suggest that a robust epidemiological analysis is required and the outcomes be disseminated regarding the type of patients generally encountered during CCAT missions. This also facilitates requirement of appropriate medical training for the personnel involved in CCAT and the equipment required. Air transport of critically ill patients is expected to rise in the future and research and innovations in this new field are advocated.

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Soil Contamination as an Indicator of Geohelminthiasis in Primary Schools in Ibarapa East Local Government Area of Oyo State

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Abstract- The study assessed the level of environmental contamination with ova of geohelminths in primary schools in Ibarapa east local government area of Oyo state. One hundred and forty-four soil samples were collected from three different spots viz toilet, classroom, and playground areas in sixteen primary schools in the study area. The soil samples were analyzed for the presence of helminth ova and larvae following standard procedures. 131 (91%) soil samples were positive after analyses, for one or more parasite stages. Hookworm larvae were the most occurring accounting for 90.2% of total parasite stages recovered from the soil samples, followed by larvae of *Strongyloides* (9.1%). Others were eggs of *Ascaris* (0.5%), Hookworm (0.1%) and *Trichuris* (0.1%). Soil samples from the toilet areas were the most contaminated and the least, though substantial, were from the playground. The low level of sanitation in the schools is reflective from the results and also suggestive of a high prevalence of infection among the pupils. The immediate need of concerned authorities in the state to improve sanitation in the schools and impose the recommended deworming regimes is critical to achieving control.

Keywords: *geohelminths, soil contamination, sanitation, antihelminthic, control.*

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I. Introduction

The spread of geohelminthiases is often associated with behavioral or cultural practices in endemic communities and are mostly found in impoverished rural areas in developing countries in the tropics (Hotez *et al.,* 2009). These diseases are part of the neglected tropical diseases and they continued to plague school aged pupils across the world. Ascariasis, Hookworm disease, Trichuriasis and, many others infect several million globally (Ogbe *et al.,* 2002). To curb this scourge, the Fifty-fourth World Health Assembly urged all WHO member states to ensure access to antihelminthic drugs where these diseases are endemic (WHO, 2003). Soil-transmitted parasites are the largest group of parasites that live in the soil during their development. Contamination of soil with parasite eggs, infective larvae, cysts and, oocysts is a direct risk factor and public health indicator of geohelminths (Saathoff *et al*., 2002). Risk factors and habits such as geophagia, nonuse of footwear, indiscriminate fecal and waste disposal, and improper sanitary and hygiene practices promote the spread of geohelminth infections (Saka *et al.,* 2014). These predisposing environmental factors are influenced by behavior with hygiene practices topping the list. Most public schools in rural communities in Nigeria do not adequately cater for toilet habits of the pupils, which promotes environmental contamination with parasite stages. In some instances, the toilets are either dysfunctional or non-existent, leaving the pupils to nearby bushes to defaecate when the need arises. Endemicity is a function of continuous contamination of the soil and frequent contact by new hosts (Mohaghegh *et al*., 2017). With this background, this study assessed soil contamination with geohelminth ova in primary schools in Ibarapa east local government area of Oyo state as an indicator of disease endemicity.

II. Materials and Methods

a) Study Area

The study was conducted among school-aged pupils in Ibarapa East Local Government (Fig.1), Oyo State, southwestern Nigeria. Ibarapa East Local Government is located between longitudes 7°45' North and 7°25' North and latitudes 3°25' East and 3°40' East. The inhabitants are majorly farmers, while others are traders and civil servants. The area had a good number of houses without toilet facilities, making the occupants visit bushes, refuse dump and mountains to defecate. Few houses in the area had modern toilet facilities. Water was usually a problem, especially during dry season, thereby making wells and boreholes the major sources of water. Information obtained from the health department of the Local Government revealed that about 70% of the children had received antihelminthic drugs in their childhood. Most of the school children go to school barefooted.

b) Ethical Considerations/Advocacy Visits

Advocacy visits were paid to the Local Government authority and the Heads of the schools where soil samples were collected before commencement. Since methodology did not involve any invasive method or human body samples, approval was given.

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c) *Study Population and Sampling*

From the study area map, six locations were selected; the two main towns; Eruwa and Lanlate and one area each from the North, South, West, and East of the local government area namely Opo-Ogede, Agasa, Dagilegbo and Owode- Adegbola respectively. Three primary schools were selected randomly by balloting from each of the six locations. However, soil samples were collected from sixteen primary schools eventually because two Nomadic schools were not available.

d) *Sample Collection*

About 500g of soil samples at 4cm depth were collected with a hand trowel at three different spots each from the playground, classroom and toilet areas in each of the primary schools and stored in clean and well-labelled polythene bags. Samples were collected between 10:00hrs and 13:00hours. In all, a total of 144 soil samples were collected and transported to the laboratory for analysis within 48-72 hours (Nock *et al.,* 2003).

e) *Larvae Extraction*

Modified Baermann Culture Technique was used for the extraction of soil nematodes. About 20g of soil was placed at the center of a double layer disposable paper towel on the bench. A pouch was formed containing the soil sample by holding the four corners of the disposable paper towel together and wrapping it around the soil sample. Rubber band was used to close the disposable paper towel pouch, and suspended in the funnel filled with lukewarm water ensuring that the soil sample was covered. The apparatus was left to stand for about 72 hours, to allow larvae actively move out of the suspended soil samples and settled at the bottom of the funnel by gravity from where it was collected with a petri dish and was viewed under the microscope using the X10 and X 40 objective lenses to check for the presence of nematode larvae (Barker, 1985).

f) *Isolation and Concentration of Geohelminth Eggs*

The samples were analyzed using a modified Zinc Sulphate ($ZnSO_4$) floatation technique. 50 g of the soil sample was mixed thoroughly with distilled water. The suspension was strained through a sieve of 150 μm mesh size to remove coarse particles. The homogenized solution was placed into sedimentation cups, filled with water, and allowed to stand for 2 hours. After the supernatant was decanted and the sediment was re-suspended with 50 mL water, it was placed in centrifuge tubes and centrifuged at 1500 rpm for 5 min. Finally, the sediment was re-suspended in 15 mL sucrose solution (specific gravity 1.2) and poured into centrifuge tubes filled to the brim; the cover slip was superimposed and allowed to stand for a few minutes with a cover slip on the tube to collect any floating egg. The cover slip was then removed and examined under the microscope at X10 and X40 objectives (Giacometti *et al.,* 2000) and examined for the presence of parasite eggs. Slides were examined microscopically and identification was done using standard keys (CDC, 2013).

III. Results

Of the 144 soil samples collected from various locations in the surroundings of the sixteen primary schools in the local government area, 131 (91%) were positive for ova or larvae of one or more parasites. Hookworm larvae were the most frequently encountered with an occurrence of 90.2%, *Strongyloides stercoralis* larvae (9.1%), Ascaris eggs (0.5%), Hookworm egg (0.1%) and *Trichuris trichiura* egg (0.1%). Six out of the sixteen schools had all the soil samples contaminated with different parasite stages (Table 1) thereby exposing the children to infection either on the playground, classroom or around the toilet areas. African Church Primary School, Opo-Ogede had the most contaminated soil samples with 265 (14.9%) hookworm larvae though soil samples from ADS Primary School 1, Ateo had the greatest diversity of parasite ova/larvae recovered with Hookworm larvae and egg, larvae of *Strongyloides stercoralis* and ovum of *Trichuris trichiura.* Soil samples from toilet areas were the most contaminated with parasites, n = 48 (47.2%). The least contaminated soil samples were from the playground area, n= 41 (31.3%), while the classroom area had 42 (32.1%) soil samples contaminated with parasite stages (Fig.2).

IV. Discussion

Over a quarter of the world population stands at risk of geohelminthiasis (Jourdan et al., 2017). The estimate is not farfetched as a part of that population will derive from the African continent largely due to little or no political will towards control. The evident unavailability or dysfunctional toilet system increases the rate of environmental contamination with the ova of these parasites by the children who see no shame *per se* in defaecating in the open. The mainstay of control of geohelminthiasis and Schistosomiasis is chemotherapy (Edelduok et al., 2013; Ohiolei et al., 2017), health education and improved sanitation (WHO, 2019). The schools investigated displayed poor sanitation as soil samples from all the premises harbored one parasite stage or the other with hookworm larvae accounting for 90.2% of stages found, and seen in all soil samples across the sixteen schools.

The playground is not immuned to contamination despite being a high activity area. Even in other climes (Mohaghegh et al., 2017), such level of contamination has also been reported among school-aged pupils. The risk of contracting infection on the playground may be higher than any of the other two

sampled sites. Most times, the children play here unsupervised and may engage in very physical plays which may, one way or the other, end up in geophagia. A very close practice to this is the habit of walking barefooted. Many of the children enjoyed playing on the grounds without shoes, a comfortable practice on a very contaminated surface, making it easy for hookworm infection and reinfection.

From the results, it is safe to predict that the prevalence of soil-transmitted helminthiasis in the schools will be high. Although 70% of the school pupils were acclaimed to have received antihelminthics, the degree of contamination suggests this may not have been effective. The recommended deworming regime by WHO is once a year, when baseline prevalence of soil-transmitted helminths is over 20%; and twice a year if infection in the community is over 50% (WHO, 2019). It was impossible to obtain consent for a population study as the local authorities were opposed to the collection of fecal samples despite processing ethical clearance. The cultural belief that collecting such samples from the pupils was a pointer to something diabolical was rampant among them, and these prevented getting actual data on prevalence.

The three sites from which soils were sampled in each of the schools predisposed the pupils to infection. Therefore infections could be easily contracted by contamination of hands or walking barefooted. Though the schools had toilets, with pit latrines featuring more than the water closet system, the practice of using it was not common among the pupils. Whether attitudinal or due to dysfunctional facilities, the level of soil contamination was high (91%) enough to provoke a bother about the level of transmission where there was no apparent attempt to improve on sanitation. At this present age, the use of pit latrines should at least be SanPlat in impoverished rural areas, and adequate provision and maintenance of the facilities ensured.

The call is on the concerned authorities to urgently improve on the sanitation in all primary schools to curb the rate of soil contamination and also abide by the recommended deworming regimes in endemic communities to achieve control.

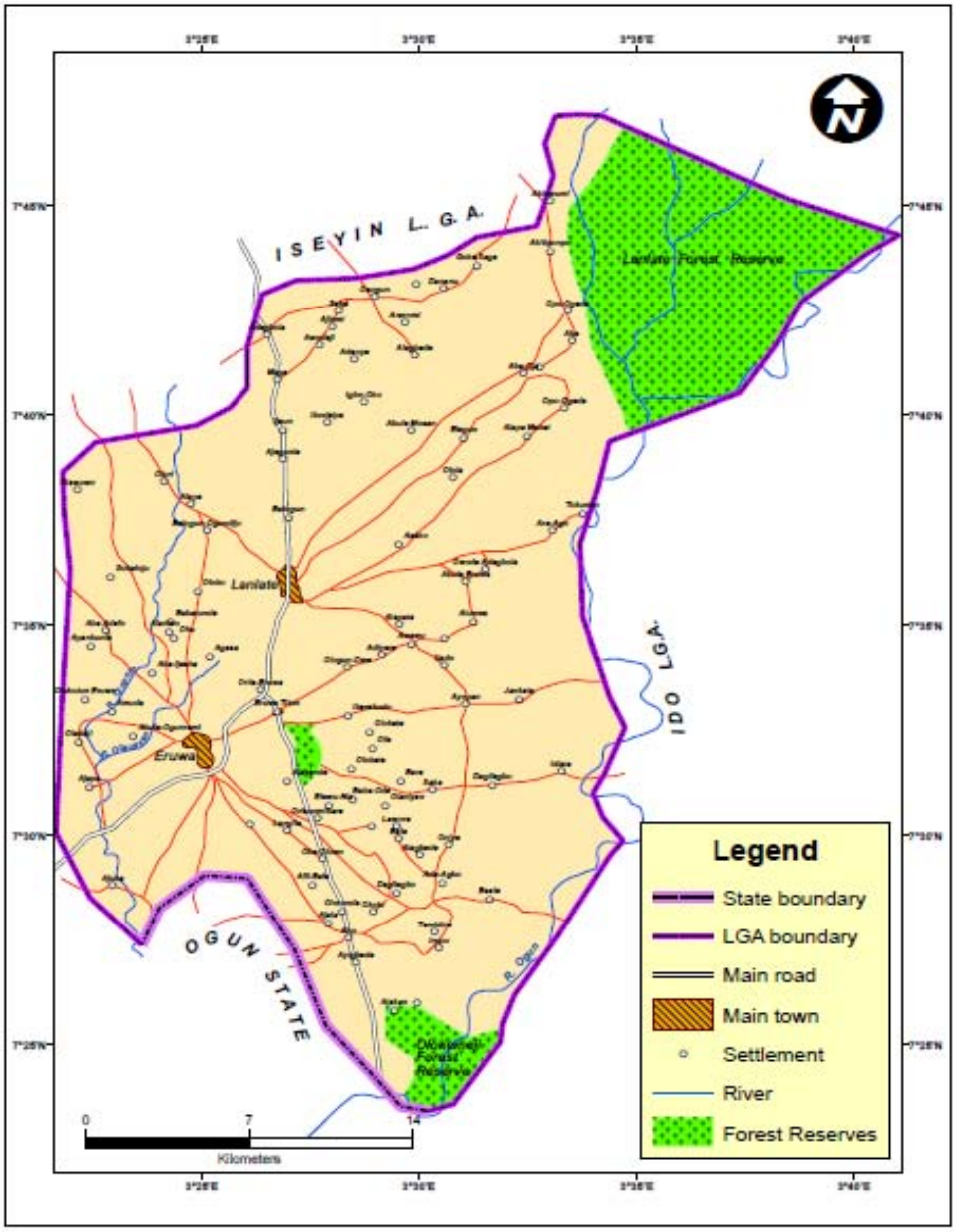

Fig.1: Ibarapa East Local Government, Oyo state

Table 1: Rate and Intensity of Soil Transmitted Parasite Stages in Soil Samples from the Sixteen Primary Schools Studied

S/No.	SCHOOLS	No. of samples examined	No. of contaminated samples (%)	*Ascaris lumbricoides* (egg)	Hookworm (larvae)	Hookworm (egg)	*Strongyloides stecoralilis* (larvae)	*Trichuris trichiura* (egg)	Total parasite count/ (%)
1	ISLAMIC PRIMARY SCHOOL, ABORERIN	9	7 (77.8)	0	70	0	29	0	99 (5.6)
2	LA PRIMARY SCHOOL 1, OKE OBA	9	8 (88.9)	0	105	0	19	0	124 (7.0)
3	BAPTIST PRIMARY SCHOOL, ISABA	9	8 (88.9)	0	95	0	17	0	112 (6.3)
4	ISLAMIC PRIMARY SCHOOL 1, AGASA	9	8 (88.9)	0	64	0	17	0	81 (4.5)
5	ISLAMIC PRIMARY SCHOOL 2, AGASA	9	9(100)	0	25	0	26	0	51 (2.9)
6	BAPTIST PRIMARY SCHOOL 1, LANLATE	9	7(77.8)	0	49	0	6	0	55 (3.1)
7	METHODIST PRIMARY SCHOOL, ATEO-LANLATE	9	9(100)	0	61	1	1	0	63 (3.5)
8	ADS PRIMARY SCHOOL 1, ATEO	9	8 (88.9)	0	107	1	13	1	122 (6.9)
9	NITECOM PRIMARY SCHOOL, MAYA ROAD	9	8 (88.9)	0	101	0	11	0	112 (6.3)
10	ISLAMIC MISSION SCHOOL, OGUNLEKE	9	8 (88.9)	0	96	0	7	0	103 (5.8)
11	BAPTIST PRIMARY SCHOOL, OKOLO	9	9 (100)	0	107	0	2	0	109 (6.1)
12	NEW COVENANT CHURCH KIDDIES ACADEMY, ABA-AYINDE	9	9 (100)	9	200	0	8	0	217 (12.2)
13	COMMUNITY PRIMARY SCHOOL, OWODE	9	9 (100)	0	75	0	0	0	75 (4.2)
14	NOMADIC SCHOOL, GAA-YUSUF	9	7 (77.8)	0	92	0	0	0	92 (5.2)
15	AFRICAN CHURCH PRIMARY SCHOOL, OPO-OGEDE	9	8 (88.9)	0	265	0	0	0	265(14.9)
16	NOMADIC SCHOOL, PANLATI	9	9 (100)	0	95	0	6	0	101 (5.7)
	TOTAL	144	131 (91%)	9 (0.5%)	1607 (90.2%)	2 (0.1%)	162 (9.1%)	1 31(0.1%)	1781

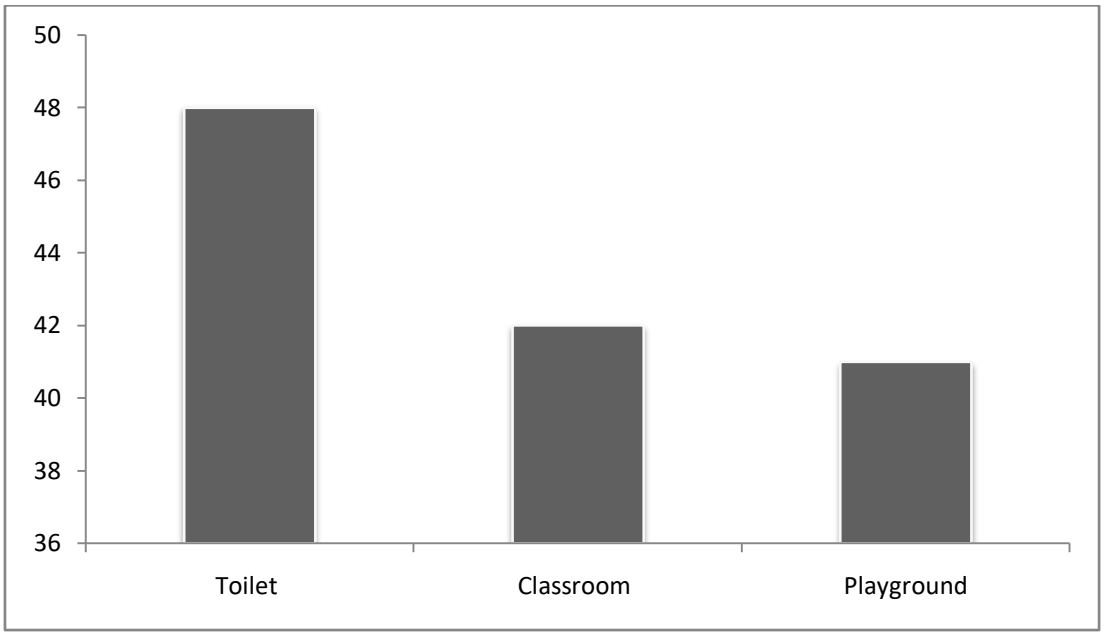

Fig. 2: Occurrence of eggs/larvae in soil samples with respect to sampled areas

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Should We Change the Therapeutic Algorithm of Type 2 Diabetes Based on Accumulating Evidence?

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In this review, we are going to discuss these mechanisms and highlight the therapeutic value of the early use of these agents instead of the long-standing traditional approach.

Keywords: type 1 diabetes; type 2 diabetes; micro-vascular complications; macrovascular complications; DPP4Is, SGLT2Is; nrf2 agonists.

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I. Introduction

Diabetes mellitus is a pandemic disease that has exponentially increasing prevalence. In 1980, 108-million persons had diabetes worldwide while in 2014, 430- million persons were affected [1]. In spite of the increased awareness about this disease and the worldwide efforts to give optimum care, 3.7 million diabetic patients lost their lives in 2012 because of diabetes and its complication [2]. This figure exceeded 5 million deaths annually in the last few years [3]. The hazard of cardiovascular mortality among diabetic patients is 2.3 folds that in non-diabetic personnel [4]. The average life span of the diabetic patients is 10-15-years shorter than non-diabetic subjects [5]. Besides, diabetes is the cause of many disabling Besides, diabetes is the cause of many disabling morbidities. In spite of the optimal management of the established cases of diabetic retinopathy that reduces the risk of visual loss by 60%, diabetes remains the leading cause of blindness among working-age adults worldwide [6]. Diabetes is the leading cause of non-traumatic lower-extremity amputation [7]. Diabetic peripheral neuropathy (PN) is the most frequent cause of sensory neuropathy [8]. Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD). One-third of T1DM develop ESRD, while only 10-20% of type 2 diabetes mellitus (T2DM) patients progress to ESRD [9, 10]. The prevalence of congestive heart failure (CHF) among diabetic patients aged 55 to 64 years is 5.5 folds the prevalence among nondiabetic personnel of the same age [11]. Diabetes is an independent risk factor for the development of ischemic heart disease (IHD). CHF and IHD are the commonest causes of death in T1DM and T2DM patients [12]. Diabetes mellitus confers a high risk of cerebrovascular stroke [13]. Endothelial dysfunction is a common pathology underlying the etiopathogenic mechanism of all these complications [14]. This endothelial dysfunction is a sequel to many metabolic changes encountered in hyperglycemic personnel. These metabolic changes include increased oxidative stress [15], hyperuricemia [16], stimulation of sodium hydrogen exchangers (NHE) [14], and stimulation of renal sodium glucose transporters (SGLT) [17].

Twenty-five years ago, the Diabetes Control and Complications Trial (DCCT) research group announced 50% reduction of microvascular complications among T1DM patients in the tight blood sugar control group compared to poorly controlled cases [18]. Five years later, the United Kingdom Prospective Diabetes Study (UKPDS) group announced similar findings among T2DM patients [19]. However, tight blood sugar control only had a marginal impact on cardiovascular disease and all-cause mortality among diabetic patients [20]. Additionally, blood sugar control using sulphonylurea compounds and insulin carries increased risk of severe hypoglycemia and weight gain [18, 19]. IN UKPDS study, T2DM patients allocated to metformin had 32% reduction for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality when compared with those prescribed sulphonylurea or insulin [21]. These favorable effects of metformin were attributed to body weight reduction and the almost absence of hypoglycemic attacks. According to these

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results and others, the American College of Endocrinology (ACE), and the American Association of Clinical Endocrinology (AACE) recommend that the choice of anti-diabetic therapies must depend on many attributes that include antihyperglycemic efficacy; risk of inducing hypoglycemia; and risk of weight gain [22]. The last 15 years have witnessed the introduction of three new hypoglycemic agents, namely, glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase 4 inhibitors (DPP4Is), and sodium glucose co-transporter-2 inhibitors (SGLT2Is). These three agents carry unique features, namely, the minimal incidence of hypoglycemic events and the favorable impact on body weight. GLP-1RA and SGLT2Is are associated with body weight reduction, while DPP4Is are weight neutral [23, 24]. Compared to older hypoglycemic agents, these newer groups carry potential favorable protective effects on endothelium, and can significantly reduce adverse cardiovascular events of diabetes in case of SGLT2Is and GLP-1RA, and are reno-protective. SGLT2Is mayalso prevent or withhold diabetic retinal complications [25]. This review will highlight the possible new strategy to prevent the development and progression of diabetic complications, the main target of this disease management.

a) The Endothelium in Diabetes

The first report on the role of the endothelium as an important regulator of local vascular tone was in 1980 [26]. The vascular endothelium is an important component of diabetic complications. Endothelial dysfunction is eminent not only in diabetic patients but also in patients suffering obesity or metabolic syndrome. Decreased synthesis of nitric oxide (NO), a potent vasodilator, is the salient feature of endothelial dysfunction. Decreased NO underlies insulin resistance by reducing insulin access to target cells [27]. Insulin has also to cross endothelial cells to reach target tissues [28, 29]. Hyperglycemia can lead to endothelial mitochondrial fragmentation and increased production of reactive oxygen species (ROS) [30]. Increased endothelial ROS is associated with increased breakdown of NO [31]. Impaired endothelial function was demonstrated within visceral fat [32], cardiac and skeletal muscles [33]. Endothelial dysfunction is associated with accelerated atherosclerosis in an animal model [34], diabetic retinopathy [35], nephropathy [36], neuropathy [37], and cerebral dysfunction [38]. To affirm the role of endothelial dysfunction in the development of diabetic nephropathy, two separate studies have disclosed that endothelial nitric-oxide synthase (eNOS) deficient mice robustly develop diabetic nephropathy [39, 40].

b) Sodium Hydrogen Exchangers

The sodium hydrogen exchangers (NHE) are trans-membrane ion channels that are responsible for intracellular pH regulation through the extrusion of hydrogen in exchange with sodium influx [Fig. 1]. NHE exist in nine isoforms [41, 42]. NHE1 is present on the surface of endothelium, vascular smooth muscle cells (VSMCs), cardiomyocytes and platelets, while in case of renal tubular and intestinal epithelium NHE3 is encountered. Activation of the NHE1 within endothelium, VSMCs, and cardiomyocytes may underlie micro-vascular and macro-vascular complications of diabetes. It can also have a role in insulin resistance and systemic hypertension. These exchangers cause increased sodium influx that stimulates sodium-calcium exchanger with consequent increase of intracellular calcium. Within endothelium, increased cytoplasmic calcium inhibits eNOS and thus decreases NO synthesis (Fig. 2). Increased intracellular calcium isalso associated with increased intracellular and mitochondrial activity of calpain, the cysteine protease, that can damage the inner mitochondrial membrane, a process that ends with cell apoptosis [43]. Activation of NHE1 in diabetic patients is a consequence of high blood glucose, insulin, angiotensin, or adipokines [44]. Endothelial NHE1 activation increasesthe influx of calcium into the cytoplasm and mitochondria associated with increased calpain enzyme activity. These changes lead to endothelial dysfunction and senescence. The development of systemic hypertension, increased insulin resistance, diabetic retinopathy, nephropathy, and neuropathy are consequences of decreased eNOS activity and accelerated endothelial senescence. It can also explain the increased frequency of vascular calcification, peripheral vascular disease, and diabetic cerebrovascular dysfunction [45]. Mitochondrial injury is associated with impaired antioxidant defense [46]. Inhibition of NHE1 using cariporide was associated with increased NO release; eNOS activity simultaneously decreased ROS production, decreased nuclear factor-κB (NF-κB) activation and decreased the production of tumor necrosis factor-α and intercellular adhesion molecule-1 [47]. Increased intracellular calcium induced by NHE1 isoform on the surface of cardiomyocytes leads to cardiac hypertrophy. Peripheral coronary ischemia secondary to endothelial dysfunction can further activate cardiac NHE1.Active NHE1 increases intracellular and intra-mitochondrial calpain that contributes to degeneration, apoptosis, and fibrosis of myocardium [44] [Fig. 3]. Activation of renal NHE3 within PCT and ascending loop of Henle causes sodium retention and can thus contribute to the development of systemic hypertension in diabetic patients [44, 48] [Fig. 4]. Activation of NHE1 on the surface of platelets plays a significant role in platelet activation. This effect is mediated through increased intracellular calcium and can contribute to the pro-coagulant state in diabetes [49]. Accordingly, activation of NHE1 on the surface of endothelial cells, VSMCs, platelets, and cardiomyocytes

beside the activation of renal NHE3 share in the pathogenesis of systemic hypertension, microvascular complications and macrovascular complications of diabetes that finally result in heart failure and ESRD.

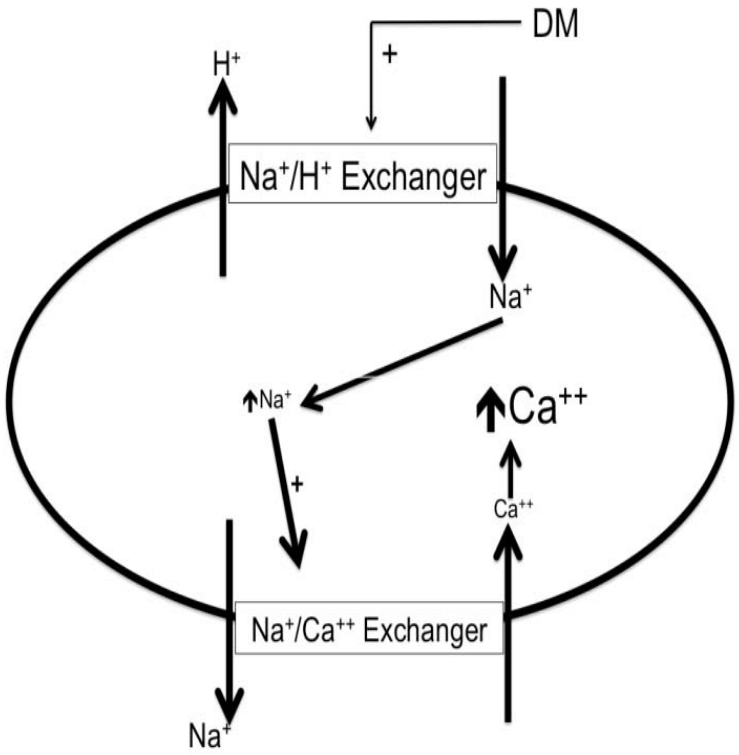

Fig. 1: Diabetic state increases the activity of the sodium/hydrogen exchanger on the surface of endothelial cells, vascular smooth muscle cells, cardiomyocytes, and tubular epithelial cells. Consequently, intracellular and mitochondrial calcium.

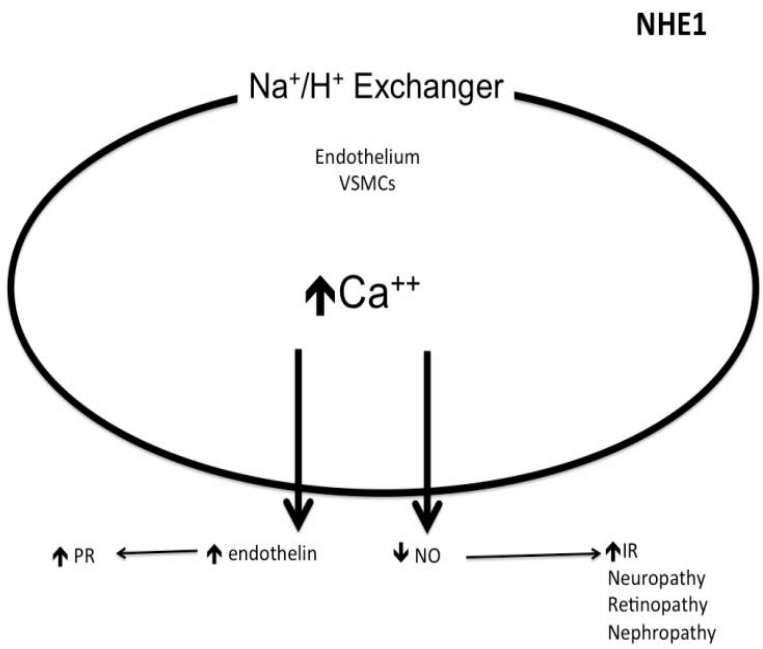

Fig. 2: Increased cytosolic calcium leads to decreased nitric oxide synthesis and increased secretion of endothelin. Increased vascular smooth muscle tone leads to increased peripheral resistance and decreased tissue perfusion. This leads to decreased insulin delivery. Endothelial damage induced by calcium can also decrease permeability of the endothelium to the delivered insulin. Decrease nitric oxide production has a role in pathogenesis of neuropathy, retinopathy and nephropathy PR= peripheral resistance; IR= insulin resistance.

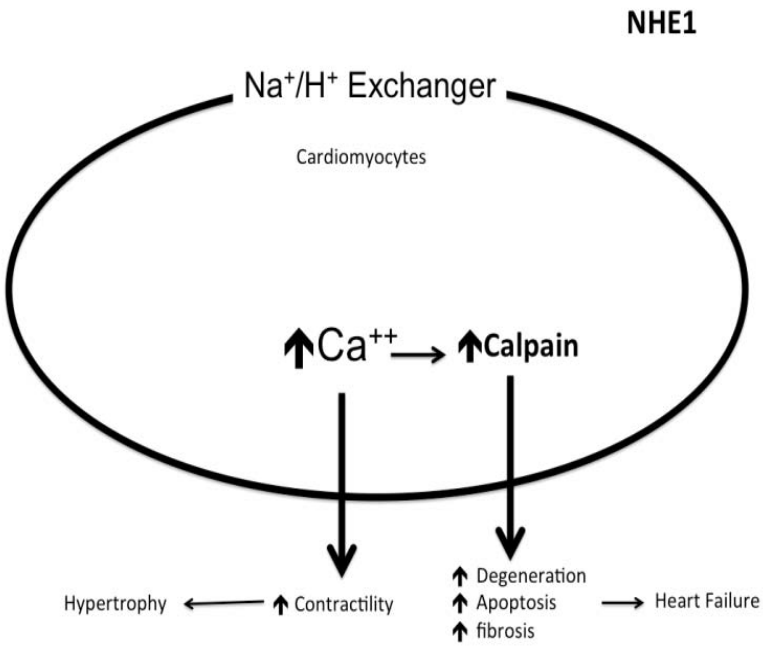

Fig. 3: Increased cytosolic calcium within the cardiomyocytes leads to ventricular hypertrophy, and increased activity of the digestive enzyme calpain. This lysolethicin digests mitochondrial membranes and results in myocardial damage that finally leads to heart failure.

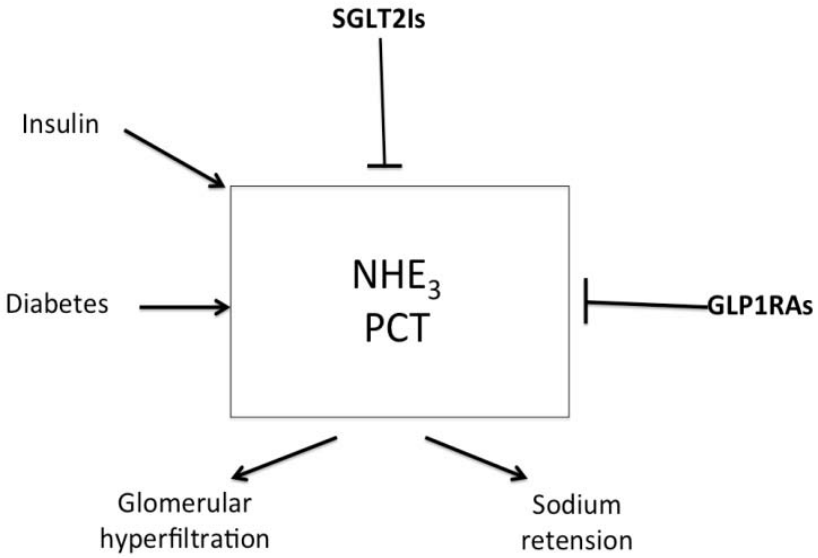

Fig. 4: Increased activity of NHE3 isomer within the proximal convoluted tubules increases sodium absorption from the lumen of these tubules in exchange with the secreted hydrogen. Decreased sodium delivery to the distal nephron segments results in glomerular hyperfiltration. Diabetic state and insulin administration increase NHE3 activity while SGLT2Is and GLP1RAs inhibit it. NHE=sodium hydrogen exchanger; SGLT2Is= sodium glucose transporter-2 inhibitors; GLP1RAs= glucagon like peptide receptor agonists.

c) Oxidative stress

Increased oxidative stress is one of the metabolic disorders encountered in diabetes. Diabetic patients have overproduction of free oxygen radicals and decreased wash out of these radicals. Increased production of free oxygen radicals is the sequel to increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [50, 51], cyclo-oxygenase [52], and lipoxygenase [53] enzymes. Hyperglycemia stimulatesall these enzymes. Sodium-glucose cotransporter 2 (SGLT2) within the brush border of the proximal convoluted tubular epithelium (PCT) is another pathway of free oxygen radicals' overproduction. Increased intracellular uric acid (UA) induces NADPH

oxidase [54]. Mitochondrial damage results in impaired antioxidant defense [46]. Increased free oxygen radicals activate NF-κB [55]. When NF-κB is free from its inhibitor, it translocates from the cytoplasm to the nucleus where it triggers the genes encoding transforming growth factor- β1 (TGF-β1), and monocyte chemo attractant protein-1 (MCP-1) and Intercellular Adhesion Molecule 1 (ICAM1) [56-58]. Reactive oxygen species (ROS) stimulate overproduction of protein kinase C (PKC) and mitogen-activated protein (MAP) kinase within mesangial cells (MCs) and pericytes. All these factors stimulate overproduction of extracellular matrix proteins [59].

d) Uric acid

Serum uric acid (UA) is a strong predictor for the development of proteinuria in T1DM patients. The risk for proteinuria increases by 80% with every 1mg/dL rise in serum UA [60]. The risk of decline of glomerular filtration rate (GFR) is significantly higher (2.4 folds) in T1DM patients with serum UA>6.6 mg/dL when compared with candidates with lower level [61]. In T1DM patients followed-up for more than 18 years, serum UA was an independent predictor of overt proteinuria [62]. In T2DM patients, 68% of the hyperuricemic versus 41.5% with normal serum UA had diabetic nephropathy (DN) [63]. Further prospective studies confirmed the increased risk of development of proteinuria and accelerated decline of GFR among hyperuricemic T2DM [64, 65]. Serum UA> 7mg/dL in males and > 6mg/dL in females were associated with a higher rate of DN progression, and overall mortality among T2DM patients that have the disease for fifteen years or more [66]. Treatment of T2DM patients suffering DN and high serum UA with allopurinol was associated with a significant decrease of urine albumin excretion (UAE) and serum creatinine and a significant increase of GFR over three years of follow-up [67]. A recent meta-analysis of 19 randomized controlled trials has confirmed the significant favorable effect of urate-lowering therapy on the rate of GFR decline. These 19 trials enrolled 992 patients [68].

Increased level of Serum UA is associated with endothelial dysfunction. High mobility group box chromosomal protein 1 (HMGB1) is a pro-inflammatory mediator synthesized and secreted by activated phagocytes or monocytes. When secreted extracellular, HMGB1 can interact with the receptor for advanced glycation end products (RAGE), inducing the production of multiple cytokines, and the induction of vascular adhesion molecules [69]. In a recent *in vitro* study, high UA concentration inhibited eNOS expression and NO production in human umbilical vein endothelial cells (HUVECs), increased extracellular HMGB1 secretion, up-regulated RAGE expression, activated NF-κB, and increased the level of inflammatory cytokines. Blocking RAGE significantly suppressed the DNA binding activity of NF-κB and the levels of inflammatory cytokines [70]. HighserumUA is also a significant predictor of systemic hypertension [71].

e) Role of glucagon like peptide-1 receptor agonists (GLP-1RA)

Glucagon-like peptide-1 (GLP-1), is a peptide hormone secreted by the neuro-endocrine cells within the mucosa of the small intestine [72]. In healthy individuals, GLP-1 activates insulin secretion, inhibits glucagon secretion and slows gastric emptying and controls apetite [72]. The susceptibility of this peptide hormone to enzyme breakdown by the dipeptidyl peptidase-4 enzyme (DPP-4) is responsible for the very short plasma half-life of GLP-1. It cannot be used therapeutically except as continuous intravenous infusion [73]. GLP-1RA are exogenous GLP-1 analogues with variable sequence similarity to the human GLP-1 [74]. The variability involved mainly two sites in the GLP-1 molecule susceptible to cleavage by DPP4; namely, alanine and lysine at positions 8 and 34 respectively. These changes, beside other modify-cations, have helped to find out many peptides that simulate GLP-1 action but with longer half-life [73]. GLP-1RAs were found to decrease body weight, and some cardiovascular morbidity, without increasing the risk of hypoglycemia [75]. Robust indications for GLP-1RAs in T2DM patients not responding to metformin monotherapy, dual therapy, or insulin include overweight, inability to control appetite, high risk of cardiovascular disease, and the need of high doses of insulin [73]. The use of GLP-1 RAs can also lower systolic, and to a minor degree, diastolic blood pressure [76]. However, long term use of GLP-1 RAs was frequently reported to be associated with increased heart rate [76, 77]. The current evidence does not support any beneficial effect of GLP-1RAs in patients with heart failure and/or impaired ventricular function [78, 79]. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was the first cardiovascular outcome trial (CVOT) of GLP-1RAs in T2DM. Based on this trial, treatment with lixisenatide in addition to conventional therapy had no impact on the cardiovascular risk in patients with T2DM and recent acute coronary syndrome [80]. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, that appeared in 2016, liraglutide use significantly decreased mortality from any cause and cardiovascular events in patients with T2DM at high risk for cardiovascular events. The benefit of liraglutide treatment is more prounced patients with eGFR <60 mL/min/1.73 m^2 and patients aged 50 years or more. In spite of these benefits, hospitalization rate for heart failure was not different between liraglutide and placebo groups [81]. Although the incidence of

retinopathy was similar in this trial, the chance of development of nephropathy was significantly lower in patients treated with liraglutide [81]. In SUSTAIN-6 trial, semaglutidewas associated with a significant decrease in the incidence and progression of nephropathy. However, a higher percentage of patients in semaglutide group developed retinopathy. Semaglutide was also associated with a 26% reduction in the hazard of cardiovascular mortality, non-fatal myocardial infarction, or nonfatal stroke [82]. In EXSCEL trial, extended release exenatide failed to show favorable cardiovascular impact [83]. This result could be due to the broader T2DM population studied in EXSCEL trial as regard to age and cardiovascular risk, the shorter follow-up period, the lower HbA1c levels and the concomitant hypoglycemic treatment (SGLT2Is were frequently used in the placebo group) [84]. A meta-analysis including nine randomized trials with dulaglutide in 6010 T2DM patients has shown that 0.67% of patients treated with dulaglutide vs. 1.18% of the placebo group developed one of the endpoints. This difference was not significant [85].

Other glucose-independent effects of GLP-1RAs include favorable effects on blood pressure, dyslipidemia, inflammation, and fibrosis. Through inhibition of renal NHE3, GLP-1RAs can promote natriuresis and diuresis. Additional effects include inhibition of the intrarenal renin-angiotensin system, inflammation, and apoptosis. The mechanism of these effects is still not recognised. Recent studies suggest important antioxidant and anti-apoptotic activities of GLP-1RAs [86] [Fig. 5].

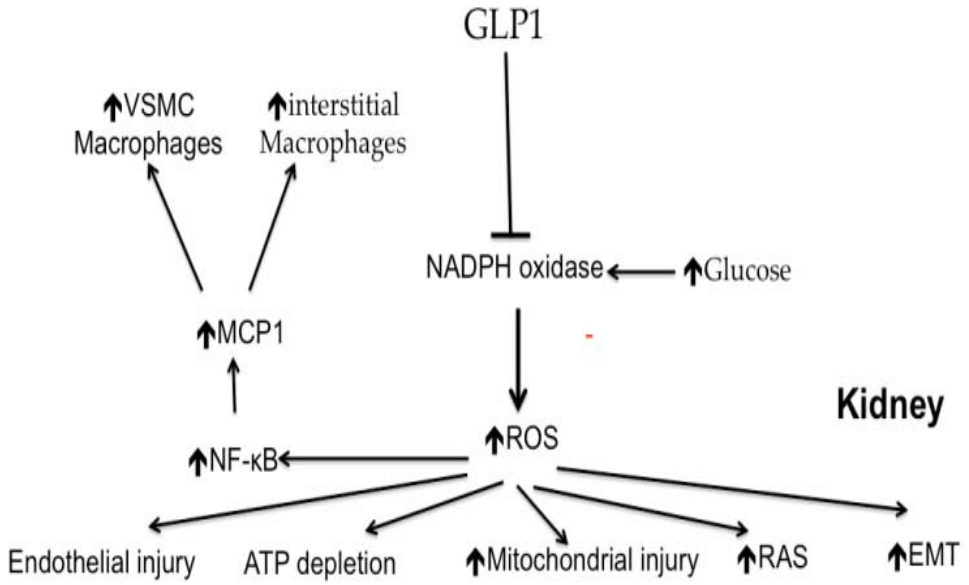

Fig. 5: Hyperglycemia stimulates NADPH oxidase enzyme within different organs including the kidney. Consequent increased production of free oxygen radicals results in increased cascade of degenerative and inflammatory processes that underlie pathology of the diabetic kidney. Glucagon like peptides inhibit NADPH oxidase and thus can muffle development or progression of diabetic nephropathy. GLP1= Glucagon like peptides; NADPH= nicotinamide adenine phosphate; ROS= reactive oxygen species; NF-κB- nuclear factor kappa B; MCP1= macrophage chemo attractantfpeptide; VSMCs=vascular smooth muscle cells; ATP=adenosine triphosphate; RAS= renin-angiotensin system; EMT= epithelial mesenchymal transition.

f) Dipeptidyl peptidase 4 inhibitors

The discovery of non-enzymatic functions for DPP4 within the kidney has attracted the attention for the reno-protective action of this hypoglycemic agent especially after disclosure of the antiproteinuric effect of saxagliptin in T2DM patients during "Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53" (SAVOR-TIMI 53) trial [87-91]. Experimental pharmacologic and genetic inhibition of DPP4 had also proven efficacy in preventing progressive renal damage in animal models of acute and chronic kidney disease [92, 93].

The glucose-lowering action of DPP4Is is through inhibition of breakdown of endogenous GLP and glucose–dependent insulinotropic peptide (GIP). These incretins improve the sensitivity of pancreatic β cells to glucose [94]. DPP4 exists in 2 forms; membrane-bound and soluble forms [95]. Membrane-bound DPP4 is present on the cell membrane of epithelial cells in the kidneys, lungs, and small intestine. It also exists on endothelial, and immune cells [96-98]. DPP4 on the surface of immune cells is also known as cluster of differentiation 26 (CD26) [97, 98]. The soluble form (sDPP4) is the consequence of shedding of the membrane-bound form. sDPP4 level increases in obese

subjects and T2DM patients and may participate in increased insulin resistance in these cases [99]. Membrane-bound DPP4 expression is triggered in case of hypoxia as well as its' shedding [100,101].

Within the kidney, DPP4 in S1-S3 segments of the proximal convoluted tubules (PCT) are linked to NHE3 and plays a role in salt and water retention through stimulation of this exchanger, NHE3 activity decreases on inhibition of angiotensin II synthesis by captopril [102], or inhibition of DPP4 [103]. Angiotensin II inhibits megalin receptor endocytosis protein expression. This process is reversed by DPP4Is [104]. Treatment with DPP4 inhibitors may reverse reduced uptake of albumin and other low molecular weight proteins by PCT [105]. DPP4 was also discovered on the glomerular endothelium and the base of the foot processes of podocytes [106]. DPP4 is expressed on T-cells, B-cells, macrophages, and dendritic cells in the kidney [98]. Stimulation of DPP4 on the surface of different immune and inflammatory cells may mediate inflammation within the kidney in diabetic patients. DPP4Is decrease inflammation in diabetes. This finding suggests inflammation as an eminent player in DPP4-mediated kidney injury [107].

However, in spite of the reduction in urine albumin excretion observed in 3 randomized controlled studies (RCT) in T2DM patients treated with DPP4Is [108-110], the only study that specifically looked for the anti-proteinuric effect of linagliptin failed to find a significant impact [111]. Moreover, DPP4Is failed to have a significant impact on doubling of serum creatinine, change in GFR, or ESRD [108-110]. On the other hand, administration of linagliptin to T2DM patients that had renal dysfunction and were prescribed ACE inhibitors or ARBs has led to additive significant reduction in albuminuria [112].

In normoglycemic milieu, microRNA-29 (miR29) suppresses DPP4 gene. In hyperglycemic state, this suppression is lost. As a consequence, cell surface DPP4 activity increases [113]. In diabetic mice, activated endothelial DPP4 induces phosphorylation of adjacent integrin β1 on the surface of the endothelium. The activated DPP4, together with the phosphorylated integrin β1 form a complex that up-regulates TGF β receptor and activates the surface vascular endothelial growth factor receptor type 1(VEGFR1). Up-regulated TGF β receptor and VEGFR1 stimulate endothelial–mesenchymal transition (EndMT) that increases transition to fibroblasts with subsequent increased fibrogenesis [114] [Fig.6]. However, the lack of significant impact of DPP4Is on GFR in human studies would cast doubts on their favorable effect on renal fibrosis in humans.

The effect of DPP4Is treatment on the retina is debatable. While some investigators reported an increase in retinal endothelial leakage and vascularity [115], others have reported a significant reduction in the risk of diabetic retinopathy progression [116].

The lack of the expected favorable effect of DDP4Is on diabetic microvascular and macrovascular complications of diabetes in spite of the proven molecular and experimental mechanisms can be attributed to potentiation of the stem cell chemokine, stromal cell-derived factor-1 (SDF-1), which promotes inflammation, proliferation and neovascularization [117]. SDF-1 enhances atheromatous plaque growth and instability, cardiac inflammation, and fibrosis [118]. The renal effects of DPP4Is are mainly through potentiation of SDF-1leading to podocyte injury and glomerulosclerosis. SDF-1 also induces natriuresis in the distal tubules, contrary to SGLT2Is and NHE3 inhibitors that act on PCT. Hence, SDF-1 cannot utilize tubuloglomerular feedback to modulate the glomerular hyperfiltration [117,119] [Fig. 7]. SDF-1 may also aggravate both retinopathy and neuropathy [117,120].

g) Sodium glucose co-transporters inhibitors

SGLT2Is constitute a recently introduced group that has insulin independent hypoglycemic effect. Three members of this group, namely empagliflozin, canagliflozin, and dapagliflozin are FDA approved and are now used worldwide. By inhibiting the upregulated SGLT2 co-transporters in the brush border of the S1 segment of the PCT, SGLT2Is can reduce the renal threshold for plasma glucose from 196 to 22 mg/dL, thereby enhancing urinary excretion of glucose [121]. They also increase distal sodium delivery and hence distal tubular sodium absorption. Increased adenosine triphosphate (ATP) consumption during sodium absorption with a consequent increase of adenosine production, causes afferent arteriolar vasoconstriction and fall in renal blood flow, reverses hyperfiltration, and accordingly reduces renal injury [Fig. 8]. In addition, SGLT2Is exert other beneficial effects, including reductions in body weight, serum UA, and blood pressure [122]. Excess glucose within the tubular lumen triggers the uric acid transporter GLUT9 within the S3 segment of the PCT and in the collecting duct to excrete UA in exchange with glucose [123]. The antihypertensive effect of SGLT2Is is related to volume depletion, loss of body weight, inhibition of endothelial NHE1 and renal NHE3, and reduction in serum UA [71].

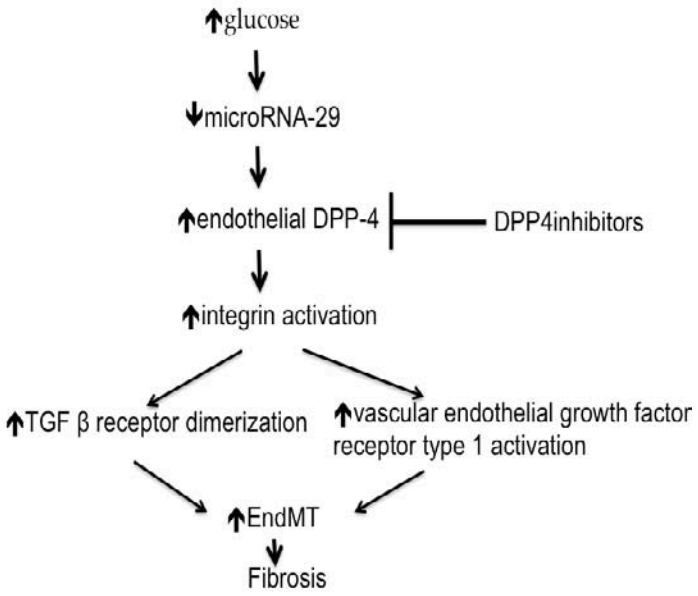

Fig. 6: MicroRNA-29 is a natural inhibitor of endothelial DPP-4 within renal vasculature. Hyperglycemia inhibits microRNA-29 and thus stimulates endothelial DPP-4. DPP-4= dipeptidyl peptidase; TGF= transforming growth factor; EndMT= endothelial mesenchymal transition.

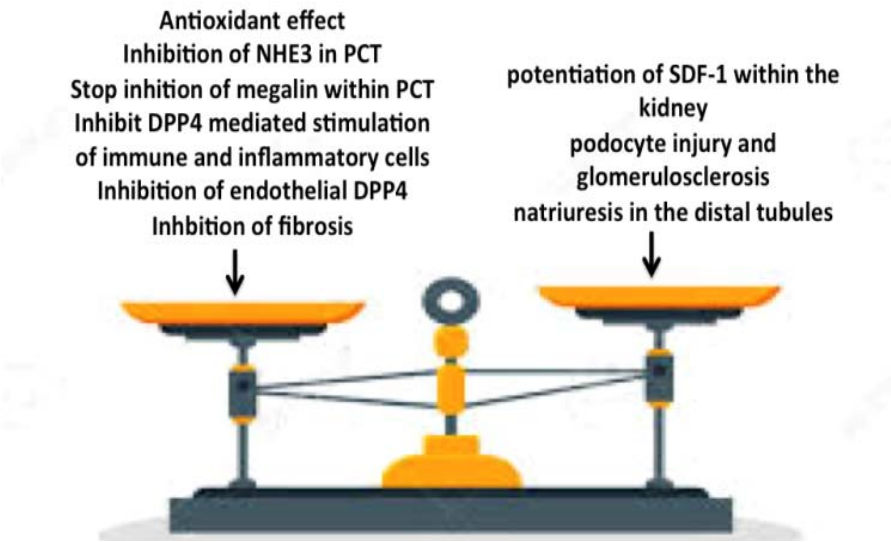

Fig. 7: The beneficial effects of DPP4Is on the kidney are muffled by the bad effect induced by stromal cells derived factor 1(SDF-1). DPP-4= dipeptidyl peptidase; TGF= transforming growth factor; EndMT= endothelial mesenchymal transition.

SGLT2Is not only decrease serum UA but they can decrease intracellular fructose metabolism and UA synthesis in the PCT epithelium [124]. Intracellular UA is pro-oxidant. It stimulates NADPH oxidase enzyme activity with consequent increase in production of ROS. This leads to premature senescence of these cells, activation of the renin-angiotensin system, epithelial-mesenchymal transition, and activation of the inflammatory cascade through activation of NF-κB [125-127] [Fig. 5]. Cyclin-dependent kinase (CDK) inhibits cell senescence. P21 is an inhibitor of CDK and thus promote cell senescence. Hyperglycemia induces P21 while SGLT2Is inhibit this factor within PCT cells [128, 129] [Fig. 9]. SGLT2Is also dampen the expression of Toll-like receptor-4, the binding of nuclear DNA for activator protein 1, the increased collagen IV expression as well as the increase in interleukin-6 secretion and interstitial macrophage infiltration induced by hyperglycemia within the renal parenchyma [130]. Moreover, fibrotic and inflammatory genes are suppressed within the diabetic kidney by SGLT2Is [131,132].

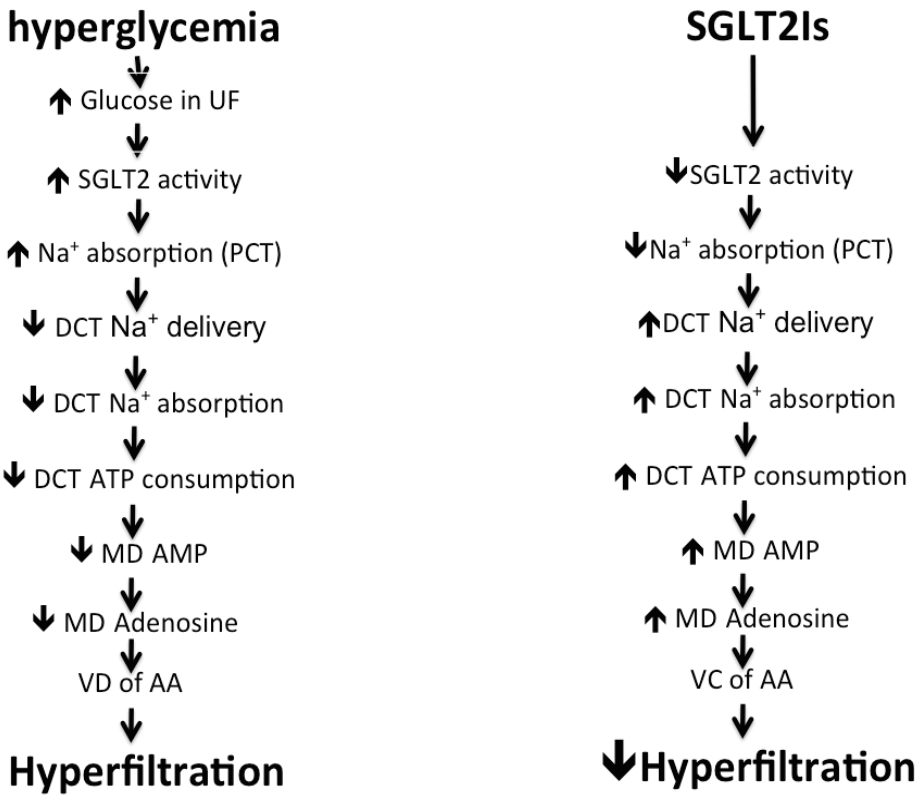

Fig. 8: Mechanism of hyperfitration induced by hyperglycemia and how do SGLT2Is control it. UF= ultrafiltrate; SGLT= sodium glucose transporter; Na^+= sodium; PCT= proximal convoluted tubules; DCT= distal convoluted tubules; ATP= adenosine triphosphate; MD= macula densa; AMP= adenosine monophosphate; VD= vasodilatation; AA= afferent arteriole;VC= vaso-constriction.

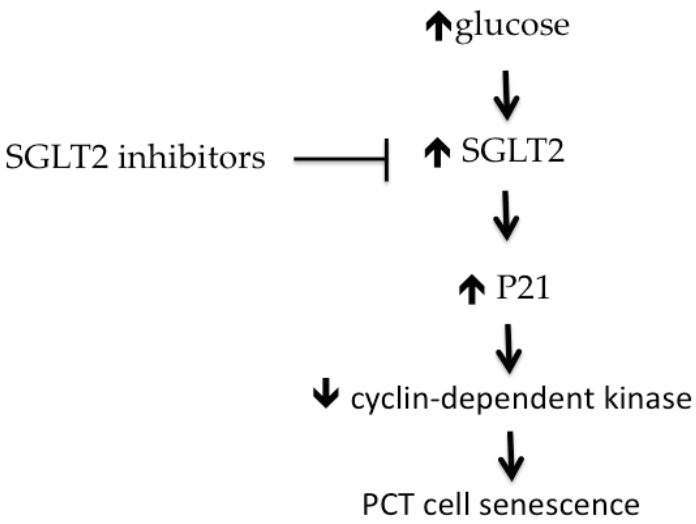

Fig. 9: Activation of SGLT2 in diabetic patients leads to over activity of P21, the natural inhibitor of Cyklin-dependent kinase 2. This kinase enzyme inhibits cell senescence. By inducing P21, diabetic patients suffer increased proximal tubular epithelium senescence. Through inhibition of SGLT2, SGLT2Is ptotect proximal tubular epithelial cells against increased senescence. SGLT=sodium glucose transporter; PCT=proximal convoluted tubule.

Through suppression of intracellular UA production, SGLT2Is inhibits renal gluconeogenesis. Intracellular UA stimulates adenosine monophosphate dehydrogenase (AMPD) enzyme and inhibits adenosine monophosphate kinase (AMPK) enzyme activities. Intracellular AMPD stimulates while AMPK inhibits gluconeogenesis [133]. In healthy personnel, the kidneys participate in endogenous glucose production.

In the fasting state, 20%–25% of endogenous glucose production takes place through renal gluconeogenesis. In T2DM, renal gluconeogenesis increases three fold [134].

Empagliflozin in EMPA-REG trial achieved 55% reduction of the chance of ESRD in T2DM patients with established cardiovascular disease, and an eGFR >30 mL/min/1.73m^2. The median observation time in EMPA-REG trial was 3.1 years [135]. In comparison, losartan treatment of similar population having DN has led toa 28% delay in the onset of ESRD during a mean follow-up of 3.4 years [136]. Empagliflozin treatment resulted in a 39% reduction of incident or worsening nephropathy, a 38% reduction in progression to overt albuminuria and a 44% reduction in doubling of serum creatinine [137]. The favorable outcome of SGLT2Is is attributable to their effect on glomerular hyperfiltration, blood pressure, body weight, and serum UA in diabetic patients [137-139]. SGLT2Is also inhibit NHEs on the surface of cardiomyocytes, endothelial cells,and renal tubular epithelial cells. NHE inhibition can explain the distinguished cardioprotective and renoprotective actions of SGLT2Is [140-142]. Decreased renal blood flow induced by SGLT2Is is related to tubuloglomerular feedback and not related to the renin-angiotensin system (RAS) blockade. Empagliflozin and dapagliflozin increase plasma aldosterone and angiotensin II [143, 144], together with increased activity of urinary angiotensin converting enzyme and angiotensin converting enzyme2 [145].

2-years treatment of T2DM patients (total of 1450 cases) already kept on metformin with either once-daily canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride titrated to 6-8 mg resulted in eGFR decline by 0.5, 0.9, and 3.3mL/min/1.73m^2/year respectively (P<0.01 for each canagliflozin group versus glimepiride) in spite of comparable reductions in HbA1c. UAE declined more with canagliflozin 100 mg or canagliflozin 300 mg than with glimepiride. These results further support that the renoprotective effect of SGLT2Is is independent of their glycemic effect [146]. Contrary to DPP4Is and sulfonylurea as that are significantly associated with increased risk of diabetic retinopathy, SGLT2Is were not associated with a higher risk of diabetic retinopathy than placebo among 100 928 patients with T2DM included in 37 independent randomized controlled trials with 1806 diabetic retinopathy events [147]. In the Canagliflozin Cardiovascular Assessment Study (CANVAS), 10 142 T2DM patients were assigned to canagliflozin or placebo. 34% of the patients had≥2 risk factors for cardiovascular events but had no history of previous cardiovascular event (primary prevention cohort), while the remaining 66% had a positive history of cardiovascular event (secondary prevention cohort). The patients were randomly assigned in a ratio of 1:1:1 to either canagliflozin 100 mg, canagliflozin 300 mg or matching placebo. After treatment for a mean of 3.6 years, the primary endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) has occurred less frequently with canagliflozin compared with placebo (26.9 versus 31.5/1000 patient-years; P=0.02). There was no statistical evidence of heterogeneity between the primary and secondary prevention cohorts. Renal outcomes were reduced by 40% and heart failure hospitalization was reduced by 33% in patients treated with canagliflozin [148,149]. 17,160 T2DM patients, including 6,974 with atherosclerotic cardiovascular disease, were assigned for 10 mg Dapagliflozin or placeboin 1:1 ratio and were followed for a median of 4.2 years. Dapagliflozin decreased the composite of cardiovascular death or hospitalizations for heart failure in those with established atherosclerotic cardiovascular disease (ASCVD) and those with only multiple risk factors. The renal composite endpoint (≥40% decrease in estimated glomerular filtration rate to <60 mL per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) decreased by 24% in the Dapagliflozin group [150]. When patients with previous myocardial infarction (n = 3,584) were specifically looked for, adverse cardiovascular events were 16% less in the dapagliflozin arm [151]. According to these studies, SGLT2Isshould be prescribed aiming at cardiovascular protection in patients with T2DM and ASCVD [152].

T2DM patients suffering CKD and albuminuria (4400 patients) were randomly assigned to receive canagliflozin100 mg daily or placebo in 1:1 ratio. All the patients had an eGFR of 30 to <90 mL/minute/1.73 m^2 and albuminuria (urine albumin/creatinine ratio>300 to 5000 mg/gm) that were receiving RAS blockers. The primary outcome was a composite of ESRD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/ 1.73 m^2), a doubling of the serum creatinine, ordeath from renal or cardio-vascular causes. The projected duration of the study was 5.5 years. Investigators of this study prematurely terminated the trial after a planned interim analysis on the recommendation of the data and safety monitoring committee. This analysis has shown a highly significant reduction of the primary composite endpoint by 34% in patients treated with canagliflozin after 2.6 years of treatment. Patients in the canagliflozin group also had a lower risk of ESRD, hospitalization for HF, and the composite of CV death, myocardial infarction, or stroke. These results indicate that canagliflozin may be an effective treatment for renal and cardiovascular protection in T2DM patients suffering CKD [153]. The observed benefits were obtained mainly in patients whose basal eGFR was between 30 and <60mL/min/1.73 m^2. The hypoglycemic effect of SGLT2Is is almost lost when eGFR is lower than 45

mL/min/1.73 m^2. In addition, these findings were observed despite very modest differences in blood sugar, weight, and blood pressure between the placebo and the active treatment groups. This suggests that the mechanism of benefit is independent of glycemic control and is likely related to the reduction in single nephron hyperfiltration related to NHE3 inhibition.

The more recent results of the DECLARE – TIMI 58 have supported the favorable effects of SGLT2Is. In this last mentioned trial, 17160 type 2 DM patients were studied using dapagliflozin 10 mg versus placebo in 1:1 ratio for 4.2 years. 47.6% of these patients had GFR >90, 45.1% had GFR between 60 and 90, while only 7.4% of the patients had GFR < 60 ml/min/1.73m^2. In addition, more than two thirds of the patients had normal urine albumin excretion. Contrary to CREDENCE trial patients where all patients were prescribed RAS blockers, only 81.3% of DECLARE study patients were on RAS blockers. The pre specified composite cardio-Renal end points (sustained decline of at least 40% in eGFR to less than 60 mL/min/1·73m^2, end-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15mL/min per 1·73 m^2), or death from renal or cardiovascular causes were significantly reduced by 24% in the dapagliflozin group while the prespecified composite renal end points (excluding the cardiovascular causes of death from the cardio-renal composite endpoints) decreased by 47%,and the chance to develop ESRD decreased by 56% in the dapagliflozin group. The significant impact of dapagliflozin was encountered in patients having baseline GFR >90, between 60 and 90, in normo-albuminuric patients, in patients with microalbuminuria and in those with overt proteinuria. We would like to emphasize that these favorable effects were only encountered in patients already maintained on either ACE inhibitors or ARBs [154].

h) Free oxygen radicals scavengers

Many preclinical studies have overwhelmed the role of reactive oxygen species (ROS) in the pathogenesis of diabetic complications. However, the less favorable outcomes of different antioxidants to prohibit the development or progression of diabetic complications in large clinical trials have dampened the enthusiasm for the use of antioxidant agents in diabetes [155]. Clinical studies using vitamin A, C, and E as antioxidant agents in pre-diabetic and T2DM patients were disappointing. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that protects and restores cell homeostasis upon activation. Although Nrf2 is activated in response to hyperglycemia, this activation does not reach the sufficient level capable to combat the oxidative stress fueled by hyperglycemia [156]. Insufficient Nrf2 activity is often associated with the pathogenesis of diabetes and its complications [157]. Natural products can activate Nrf2, as a potential therapeutic target to control diabetic complications [157, 158]. Cruciferous vegetables, grapes, buckwheat, black tea, citrus fruits, apple peels, cinnamon, turmeric, Berberis Mahonia plant, kiwi fruits, the climbing plant Sinomenium acutum, garlic, and Bitter Melon are rich sources of different natural Nrf2 activators [159-162].

Consumption of 10 gms of broccoli sprouts powder, a rich source of sulforaphane, daily for four weeks was associated with significant improvement in insulin resistance in sixty-three T2DM patients [163]. In a double-blind trial in T2DM patients, the study candidates consumed oral 2×5 mg resveratrol (resveratrol group) or a placebo (control group) for four weeks. Resveratrol significantly decreased insulin resistance, and urine ortho-tyrosine/creatinine ratio as an index of ROS production [164]. A more recent study of ten T2DM subjects, daily consumption of 3 grams of resveratrol for 12 week has increased skeletal muscle Sirtuin1 and adenosine monophosphate kinase enzymes expression. These findings can further support the insulin sensitizing effect of resveratrol [165]. On the other hand, resveratrol supplementation over five weeks in fourteen T2DM patients already kept on diet control did not have a significant effect on glycemic control [166].

In seventy-five patients undergoing primary cardiovascular disease prevention, resveratrol-rich grape supplement significantly decreased high-sensitivity C-reactive protein, tumor necrosis factor-α, plasminogen activator inhibitor type 1, and increased anti-inflammatory interleukin-10. The authors concluded that 1-year consumption of a resveratrol-rich grape supplement improved the inflammatory and fibrinolytic activities in high cardiovascular risk and diabetic patients [167]. The beneficial anti-inflammatory effect of resveratrol-rich grape supplement was further supported in a later study of 35 T2DM male patients. One-year consumption of resveratrol-rich grape supplement down-regulated the expression of pro-inflammatory cytokines in circulating mononuclear cells [168]. However, a more recent and larger study failed to prove a significant impact of low (40 mg/day) and high doses (500 mg/day) used for 6 months on fasting blood sugar, glycated hemoglobin or c-reactive protein [169]. When 36 dementia-free, T2DM 49-78 years old patients consumed single doses of synthetic trans-resveratrol (75, 150 and 300 mg) at weekly intervals, trans-cranial Doppler ultrasound both before and 45 min after treatment had shown that only the 75 mg dose was efficacious to improve the cerebral vasodilator responsiveness in both middle and posterior cerebral arteries [170]. In addition, a single 75 mg dose of resveratrol was found to improve neurovascular coupling and cognitive performance in Thirty-six T2DM

adults aged 40-80 years [171]. A more recent study has shown that a daily 100mg resveratrol supplementation for twelve weeks in 50 T2DM patients was associated with a significant decrease of arterial stiffness estimated by cardio-ankle vascular index [172].

When the endothelial function was assessed using digital volume plethysmography to measure the changes in the reflective index, oral intake of curcumin 150 mg twice daily for eight weeks has lead to a significant improvement in endothelial function [173]. Supplementation of twenty T2DM patients suffering overt proteinuria with 22mg of curcumin three times daily for two months significantly decreased urinary protein excretion and urine IL-8 beside serum levels of TGF-β and IL-8 [174]. Curcumin 500 mg three times daily was administered for nine months to 120 pre-diabetic patients and significantly improved insulin resistance and beta cell function with consequent prevention of diabetes [175]. Further studies supported the favorable anti-diabetic effect of curcumin [176-178].

i) Recommendations of diabetes associations

In October 2018, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) issued an updated consensus statement on management of hyperglycemia in T2DM patients. This consensus showed-up during the annual meeting of EASD in Berlin, Germany. In this consensus, patients with clinical CV disease should receive one of SGLT2Is or GLP-1RAs, while in patients with CKD or clinical HF and ASCVD, SGLT2Is should be considered [179]. The choice of diabetes therapies as recommended by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) must be individualized based on many attributes including the risk reduction in heart and kidney disease [180].

j) Novel markers of Diabetic complications

Mannose-binding lectin (MBL) is a recognized protein of the innate immune system. It is composed of a lectin (carbohydrate-binding) moiety attached to a collagenous moiety. MBL binds to a wide range of sugars that permits MBL to interact with a wide range of viruses, bacteria, yeasts, fungi, and protozoa containing such sugars within their cell walls or membranes. When bound to its target sugar moiety, MBL can activate the complement system in the classic pathway or in C1-independent manner [181]. MBL is independently associated with HbA1c among diabetic patients [182]. MBL is involved in complement activation within the diabetic kidney [183] and was discovered as a possible independent predictor of DR, DN and other vascular complications in type 1 and type 2 diabetes [184-189].

In 297 newly diagnosed T2DM patients, serum fibrinogen was a strong predictor for DN [190]. Serum Adiponectin was proved as a strong predictor of DN in both type 1 and type 2 diabetic patients according to a recent meta-analysis of 13 studies of more than five thousand cases [190].

II. Discussion

Diabetic complications pose a massive public health and economic burden. The introduction of GLP1RAs, DPP4Is, and SGLT2Is has revived the hope to effectively prevent or slow down the rate of progression of these complications. These hypoglycemic agents have, in addition, a favorable effect on body weight with less likelihood to experience hypoglycemia. In parallel with their evolving evidence of CV and renal protective effects, ADA recommended SGLT2Is as second-or third-line antihyperglycemic treatment [191]. The updated consensus statement on management of hyperglycemia in type 2 diabetes issued by EASD and ADA has also recommended the early introduction of SGLT2Is and GLP1RAs to diabetic patients with clinical CV disease and SGLT2Is to patients with CKD or clinical HF and ASCVD. These recommendations were founded on the accumulating evidence of the significant impact of these agents in secondary prevention. The lack of similar significant impact in primary prevention is likely related to the relatively short duration of CVOTs. The most famous primary prevention trial in T2DM patients is UKPDS. It took ten years after the end of this study to get significant differences in acute myocardial infarction and overall mortality between intensive therapy group and the standard of care group [192]. In spite of the significant renoprotective effect of canagliflozin in CREDENCE trial in the whole studied group, patients with eGFR≥ 60 mL/min/1.73 $m^2$and patients with UAE ≤1000 mg/gm creatinine failed to get the expected benefit [153]. The planned duration of this study was 5.5 years. However, the study was prematurely terminated according to the observed significant difference in the composite endpoints between the 2 arms in the whole group. Given the known long duration of stage 4 DN, the short duration of this study was not enough for patients recruited with eGFR≥ 60 mL/min/1.73 m^2 and patients with UAE ≤1000 mg/gm creatinine to d evelop enough number of primary endpoints. The rate of decline of GFR in DN patients is around 6mL/min/1.73m^2 [146]. The more recent results of the DECLARE – TIMI 58 did support this view. This last mentioned trial continued for 4.2 years. In this study, the significant impact of dapagliflozin was encountered in patients having baseline GFR >90, between 60 and 90, in normoalbuminuric patients, and in patients with microalbuminuria. These favorable effects in patients of DECLARE study are likely related to the relatively longer duration of follow-up [154]. Taking these results into account and according to the accumulating evidence, more energetic primary preventive studies should be designed. These new studies should select newly

diagnosed diabetic patients that have laboratory markers of likelihood to develop diabetic nephropathy later during the future course of their disease. The main obstacle for such studies is the duration needed to have enough number of endpoints for adequate statistical analysis. Such long duration may lend such studies very costly and very exhaustive. Given the safety and non-inferiority of SGLT2Is, GLP1RAs, and DPP4Is, and the highlighted beneficial effects of these agents, we suggest a more reproducible approach to manage T2DM patients. In addition to T2DM patients with clinical CV disease, and those with ASCVD, patients with high cardiovascular risk should be prescribed SGLT2Is as second-line hypoglycemic agent after metformin. RAS blockers should be additionally added to guarantee optimum benefit. In the case of morbid obesity, inability to control food avidity or hyperglycemia, GLP1RAs can be used instead of SGLT2Is. In case of failure of SGLT2Is to achieve the glycemic target, either DPP4I or GLP1RA should be added as the third-line agent. SGLT2I can be added on top of GLP1RA if the later failed to achieve the glycemic target. Routine screening of diabetic patients for likelihood to develop diabetic nephropathy using the early predictors like serum MBL, fibrinogen, or adiponectin can help to select patients prone to develop diabetic nephropathy. These patients should be prescribed SGLT2Is to prevent the development of the disease instead of waiting untill they develop albuminuria. This primary prevention approach can completely abort the development of DN instead of the current secondary prevention that just postpones the event for few months or years.

Conflict of Interest

The authors have nothing to declare.

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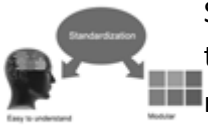

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2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research 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.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

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.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- 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.

Title page:

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.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

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.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

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Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
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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