UNIVERSITY
OF TURKU

Emerging technologies and materials in female hormone monitoring

Materials engineering

Bachelor's thesis

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6.5.2024

Turku

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Subject: Materials engineering
Author: Jerry Ylinen
Title: Emerging technologies and materials in female hormone monitoring
Supervisor: Doctoral researcher Naela Delmo
Number of pages: 25 pages
Date: 6.5.2024

In health research and technology, understanding female physiology and hormones is important. Importance is underlined with the underrepresentation of women and the increasing need for rapid development in the field. This thesis introduces the crucial role of the four main hormones: luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogens and progesterone, with a focus on estradiol as primary estrogen. Female hormone monitoring extends to fertility, hormonal assessment, drug dosing, and overall health and wellbeing monitoring.

However, traditional science is often male dominated. This has led to an imbalance in health research. Female physiology and hormones have not been considered enough, resulting in challenges particularly in medication development. Here, male-centric data is typically extrapolated for all patients, and this has led to side effects on female patients. Technical challenges and the lack of at-home female hormone monitoring are conceded mainly due to the lack of accurate and non-invasive methods in the market.

To address these issues, the thesis goes into the emerging technologies and materials to further advance the field. Wearable sensors are promising technological devices for continuous monitoring, while material development offers enhanced sensor sensitivity and selectivity. Materials combined with nanoparticles or biological elements offer potential for developing highly sensitive hormone sensors.

The objective of this document is to highlight the need for advancements in female hormone monitoring, present new methods and technologies, and explore new materials in the field. By comprehensively going through the current state of the female hormone monitoring field and technologies, this study aims to give information about the challenges and opportunities for future directions.

Key words: luteinizing hormone, follicle stimulating hormone, progesterone, estrogen, estradiol immunoassay, chromatography, wearable sensors, sampling, invasive, non-invasive, graphene, carbon nanotube, aptamer.

Kanditutkielma

Oppiaine: Materiaalitekniikka
Tekijä: Jerry Ylinen
Otsikko: Emerging technologies and materials in female hormone monitoring
Ohjaaja: Väitöskirjatutkija Naela Delmo
Sivumäärä: 25 sivua
Päivämäärä: 6.5.2024

Terveystutkimuksessa ja -teknologiassa naisten fysiologian ja hormonien ymmärtäminen on tärkeää. Tämä on tärkeää, koska naiset ovat aliedustettuina ja alalla on tarve nopealle kehitykselle. Tässä kandidaattityössä käsitellään neljää tärkeintä naisten hormonia: luteinisoivaa hormonia (LH), follikkelia stimuloivaa hormonia (FSH), estrogeenia ja progesteronia., keskittyen ensisijaisesti estradioliin pää estrogeenina. Naishormonien seuranta ulottuu hedelmällisyyteen, hormonaaliseen monitorointiin, lääkkeiden annosteluun sekä yleisen terveyden ja hyvinvoinnin seurantaan.

Perinteinen tiede on kuitenkin usein miesvaltaista. Tämä on johtanut epätasapainoon terveystutkimuksessa. Naisten fysiologiaa ja hormoneja ei ole otettu riittävästi huomioon, mikä on johtanut haasteisiin erityisesti lääkekehityksessä. Lääkekehityksessä on ekstrapoloitu mieskeskeistä dataa, mikä on johtanut sivuvaikutuksiin naispotilailla. Tekniset haasteet ja naishormonien kotiseurannan puute johtuvat pääasiassa siitä, että markkinoilla ei ole tarkkoja ja ei-invasiivisia menetelmiä.

Näiden ongelmien ratkaisemiseksi tutkielmassa tarkastellaan uusia tekniikoita ja materiaaleja, joiden avulla alaa voidaan kehittää edelleen. Puettavat sensorit tarjoavat lupaavia tekniikoita jatkuvaan seurantaan, kun taas materiaalien kehittäminen parantaa sensoreiden herkkyyttä ja selektiivisyyttä. Nämä materiaalit yhdistettynä nanohiukkasiin tai biologisiin elementteihin tarjoavat mahdollisuuksia kehittää erittäin herkkiä hormoniantureita.

Tämän työn tavoitteena on korostaa naisten hormoniseurannan kehittämistarvetta, esitellä uusia menetelmiä ja teknologioita, sekä tutkia uusia materiaaleja. Naishormoni seurannan ja tekniikoiden nykytilaa käydään läpi. Työssä pyritään myös antamaan tietoa tulevaisuuden haasteista ja mahdollisuuksista.

Avainsanat: luteinisoiva hormoni, follikkelia stimuloiva hormoni, progesteroni, estrogeeni, estradioli, immunomääritys, kromatografia, puettavat sensorit, näytteenotto, invasiivinen, ei-invasiivinen, grafeeni, hiilinanoputki, aptameeri

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1 Introduction

1.1 Introduction to the topic

In an era marked by rapid advancements in health research and technology, the need to delve more into female physiology and hormones has become increasingly necessary. Numerous hormones play a vital part in female physiology, but four stand out: luteinizing-hormone (LH), follicle-stimulating hormone (FSH), estrogens and progesterone. Figure 1 shows the structure of estradiol, the most potent form of estrogen, and progesterone.

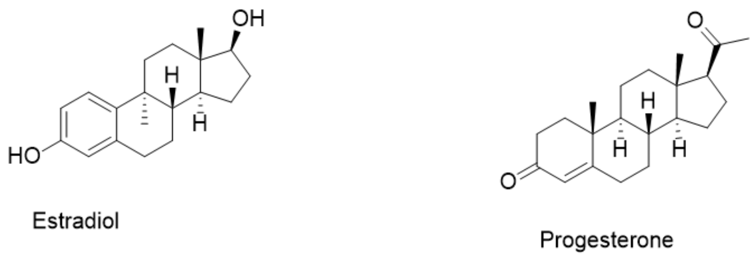

Figure 1. Structure of estradiol and progesterone, drawn using ChemDraw by Jerry Ylinen.

Female hormones affect every field of life, and with the help of hormone monitoring it can be improved. Importance of female hormones lie in the multiversal information they provide. Hormone monitoring can help with multiple problem points such as: detecting best days of fertility, hormonal imbalances, drug dosing, overall health, and wellbeing. All the mentioned methods could be improved and made remarkably more accurate with the help of better monitoring.

In traditional science, the field is male dominant. This causes a lot of issues with the imbalance of studied sexes. Female physiology and hormones are not taken enough into consideration in health research, and it can cause challenges. Most common issues emerge in medication development. Historically, the test cells and subjects are mostly male, and this can cause women to have negative responses to the medication [1].

Technical challenges of at home female hormone monitoring is caused by the lack of it. Female hormones nowadays cannot be measured accurately at home or without the need of a health specialist. Hormone levels constantly change, and the measured amount can be low. Hormones can be difficult to measure from invasive samples since they have compositions that can make the measurements inaccurate. These compositions include proteins, fats and other molecules that can make the measurement process more difficult. To gather accurate information, conventional methods such as immunoassays and chromatography are needed.

Female hormone monitoring devices could help all parts of life and give accurate information about hormonal changes during the day and throughout the menstrual cycle. This data could further be recognised as reasons for certain responses from the body. The data flow can be enhanced with optimal materials such as graphene that allow the sensor technology to work correctly. Current female hormone monitoring is restricted to lab tests and home test kits. Laboratory tests most commonly need a blood sample which can be uncomfortable for most. Current efforts in the hormone monitoring could solve that issue by using non-invasive sampling techniques as the basis for the testing. The technologies could also allow the gradual minimalization of the devices and could bring accurate and personalised female hormone monitoring.

1.2 Objectives and motivation

The purpose of this document is to gather information about the need for existing methods, as well as new technologies and materials that could improve female hormone monitoring. It gives the reader a general view of the state of female hormone monitoring and the technicality of it. The thesis aims to highlight the need for new materials and presents multiple new ways that the area could be improved.

Subject of the thesis was picked since the field of female hormone monitoring is still small, caused by multiple factors and mostly due to lack of technical innovations, and could be improved plenty. In line with this is the personal interest on the subject, and the fact that it could improve half of the population’s health and wellbeing.

This thesis investigates current state of female hormone monitoring and the up-and-coming technologies and materials. The materials discussed are carbon nanomaterial- and biological-based materials. Importance of such are based on working principle and benefits they have. Thesis goes through the pros and cons of emerging technologies and the challenges they face. Furthermore, this thesis tries to give a clear picture of the overall state of female hormone monitoring and the reasoning why it should be studied more.

The thesis answers the following questions:

1. Why is female hormone monitoring in the need for rapid development?
2. What are the possible methods of measuring female hormones in the future?

1.3 Structure of the thesis

The thesis is assembled of an introduction, four sections and a summary. Introduction works as a brief overview to the topic and presents the objectives and motivations of the thesis. First content part goes through the current state and problems with gender inequality and presents the need for female hormone monitoring. Some conventional methods are presented in the second chapter. Third part is based on the emerging technologies. Fourth content part goes through the materials and the basic principles of them. Finally, the thesis is closed off with a summary.

2 Current state and problems with gender inequality in health research

Gender inequality persists as an issue in multiple fields, especially in health research. Despite several advancements in the field there are still some issues that remain, particularly gender representation in research studies.

2.1 Underrepresentation of women in health research

The underrepresentation of women in clinical studies remains problem and male participants often outnumber women. Disproportion of the genders leads to unequal representation in the studies. Statistics indicate that women are usually misrepresented in the studies, and this can be harmful especially when trying to look for exceptions in female participants.

Historically, females have been excluded from clinical research, with women typically making up to 29-34% of the research participants. [2] This is due to the practice of generalising data from men to analyse both sexes. Additionally, the inequality has also been pressured by financial and legal risks. These risks include the risk of pregnancy and different adverse effects. [3]

The consequences of this underrepresentation are significant. Women may experience delays in diagnosis and treatment, which can lead to potential misdiagnoses and other harm. [4] This is due to the assumption of gender homogeneity when it comes to treatment and body responses. This has had a negative effect on the amount of research done based on female physiology. This has resulted in certain medications having a negative effect or responses to female patients.

Concerns about the potential impact on pregnancy have also led to the exclusion of women from certain studies. Unknown responds to pregnancy are too big of a risk for a company to take. This has resulted in certain studies to rule out women completely from the studies.

2.2 Importance of hormone monitoring in health research

Monitoring hormone levels is important in the early recognition of specific diseases. Often in cardiovascular diseases, reproductive disorders, and autoimmune conditions, hormone levels can fluctuate. This underscores the importance of gender-specific research, as some diseases affect women differently. Examples of the diseases include cancers and especially lung cancer. Women have a 20%-70% higher likelihood of developing lung cancers compared to men. [5]

Gender specific differences in physiology, pharmacokinetics, and pharmacodynamics have an impact on, for example, drug absorption and metabolism. Hormones can modulate receptors and enzyme activities which affect the drug efficiency. Hormones, like testosterone and estradiol affect pharmacokinetics and -dynamics. This can affect certain drugs and how they work. Drugs are also designed for a certain benchmark body that women do not usually fulfill. Drug doses can be too high due to the differences between body compositions of men and women. [6]

Acknowledging the differences between the genders could significantly alter the results of treatment response and overall health. By taking hormonal variations to account in treatments, risks related could be mitigated. This could lead to more optimized outcomes while reducing the chance of negative effects.

3 Conventional ways of measuring hormones

There are multiple ways of measuring hormones. The following sections will give a simplified summary on how the conventional methods work as well as their advantages and limitations. The choice of methods depends on multiple factors such as cost, practicality, and molecule of interest. [7]

3.1 Immunoassays

Immunoassays are biochemical tests used to detect or quantify a substance. They work by recognizing molecules of interest via specific antibody-antigen binding, as shown in figure 2. The immune system's ability to bind to foreign substances and are widely used in diagnostics, research, and various health care industries. Immunoassays have multiple applications such as the detection of hormones.

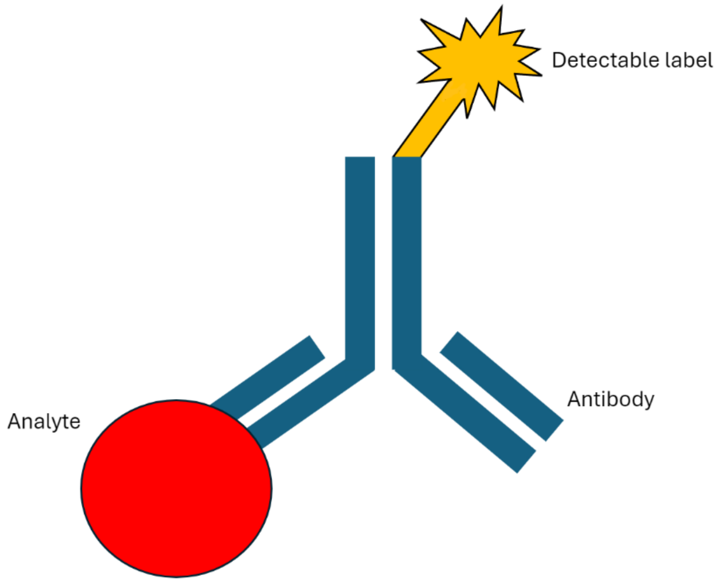

Figure 2. Basics of recognising molecules via antibody-antigen interactions. Drawn using PowerPoint by Jerry Ylinen.

3.1.1 Enzyme-linked immunosorbent assay (ELISA)

ELISA is a test that works based on certain antibody-antigen interactions and how the components attach on to the solid phase microtiter plate. It uses four methods to measure soluble hormones which are as follows: sandwich, competitive, direct, and indirect. Variety in the methods comes from the way the antibodies are attached on a plate and how they are detected. ELISA tests can be qualitative, quantitative, or semi-quantitative,

In direct ELISA, the solid phase plate is covered with antigens which are bound to the plate via incubation. Matching antibody buffer is added with conjugate enzymes that bind to the antigens. Substrate for the specific enzyme is added. Usually, the substrate is colour changing and the colour change will be detected. The colour change depends on how strong the reaction is.

In indirect ELISA, the steps are same as in direct ELISA, apart from adding an enzyme-linked antibody that is complementary to the primary antibody. After the secondary enzyme-linked antibody is added the steps are the same.

In sandwich ELISA the surface of the solid phase plate is covered with known antibody. After that, that antigen sample is added that attaches to the antibody surface. After that, a primary antibody is added that attaches to the antigen, further the secondary enzyme linked antibody is attached. Then a substrate is added to produce detectable source.

In competitive ELISA, the antibody is incubated with the presence of the antigen that is known. Then the incubated complexes are added to the surface of the plate. After that the secondary enzyme linked antibodies are added. After that, a substrate is added to produce detectable source. [8],[9]

3.1.2 Radioimmunoassay (RIA)

RIA uses a radioisotope bound to an antigen. It is used to measure substances in blood and saliva. The working principle is that the radioisotope bound antigen attaches to a certain antibody and then a competitive target antigen is added. The target antigen replaces some of the radioisotope bounds antigens. After the target antigens are attached the amount of radioactive signal is measured. The radioactive signal tells how much of the target antigen is present since the original amount of radioactive signal is known. This method is extremely sensitive and specific and remains in use even though it uses radioactivity. [7]

RIA is commonly used as a gold standard measurement for follicle-stimulating hormone (FSH). However other methods such as highly sensitive ELISA are developed, because of its use of radioactivity and a large sample. [10]

3.1.3 Fluoroimmunoassay (FIA)

FIA uses antibodies which are labelled with fluorescent probes. Labelled antibodies bind with targeted antigens via incubation and form complexes. Antibody-antigen complexes release UV light with the help of fluorescent compounds. Then the antibody-antigens are isolated, and the amount of UV light can be measured and detected. It is an extremely sensitive and fast measurement method and is used widely in in vitro testing. [7]

3.2 Chromatography

Chromatography is a technique used to separate certain substances from a mixture. It is based on a distribution in two phases: stationary and a mobile phase. [11] The chromatographic system is made from a mobile phase pressure system, injector system, column, detector, and a read-out system, as shown in figure 3.

Figure 3. Basic working principle of chromatographic system. Drawn using PowerPoint by Jerry Ylinen.

Chromatography methods paired up with mass spectrometry can be used to quantify hormones. Especially solid-phase methods are used for endogenous estrogens. This is due to the small volume of corresponding metabolites in serum, plasma and saliva. Mass spectrometry is essential for studying similar hormones, because related molecules can bind to the same ion. [12]

3.2.1 Liquid chromatography (LC)

In LC the mobile phase is a liquid. The liquid mixture is passed through the stationary phase and the substances interact differently with the stationary and mobile phase. These interactions cause them to be separated. Separation is based on the substance’s chemical interactions. [13]

Two of the following chromatography techniques are also combined with mass spectrometry. Mass spectrometry is used to detect and identify the substances in this context. [14]

3.2.2 Liquid chromatography - mass spectrometry (LC-MS)

When the LC process is completed, the substances are ionized. Then, they are measured with a mass analyser based on mass ratio relevant to the charge they have. With the help of MS, the substances can be more accurately identified.

3.2.3 Gas chromatograph–mass spectrometry (GC-MS)

The working principle of GC-MS is same as in LC-MS, but the mobile phase is a gas. After the separation in stationary phase the process is identical. Biggest difference is the gas mobile phase that allows for quicker separation and is cheaper compared to the solvents used in LC-MS.

4 Wearable Sensor Technologies

Wearable sensors are devices attached to the body, allowing for continuous sensing for variety of changes. These are specifically designed to measure body activity and, in this instance, hormones. Wearable sensors are built in with the detection system and can in some cases display the gathered data, as seen in sport watches.

Sensors detect changes in physical, chemical, biological, or environmental conditions. In chemical sensing, the analyte is detected with a device selectively. The devices consist of a recognition layer and a transducer, as shown in figure 4. The recognition layer serves as the interface in between the analyte and the transductor. It generates an input signal, which is transmitted to the transducer. When the transducer receives the input signal, it transforms it into an output signal that can be detected. The output signal provides information about the amount of analyte present in the sample. [15]

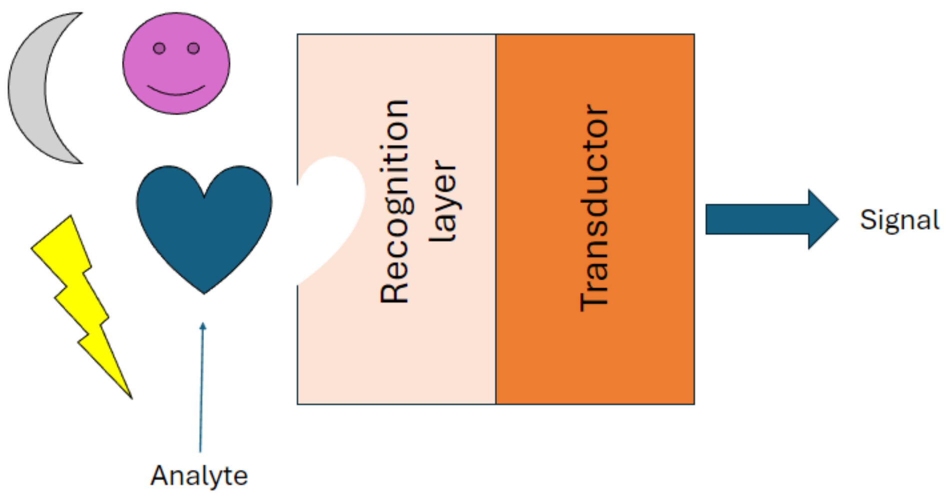

Figure 4. General working principle of a sensor. Drawn using PowerPoint by Jerry Ylinen.

4.1 Sampling techniques

One important aspect in wearable device technology is the collection of biological samples for analysis. Here, the traditional invasive method and emerging non-invasive procedures are discussed.

4.1.1 Invasive

Invasive sensors penetrate the skin, often using micro-needles, accessing bodily fluids such as blood. This allows the collection of samples that can be then detected to receive data. Invasive methods are usually very sensitive due to the direct access of bodily fluids. They are usually very reliable since they are affected less by external factors. However, the presence of a variety of compounds besides the target hormone can potentially affect the accuracy of the measurement. [16]

Invasive methods can allow continuous monitoring, offering continuous data about hormonal fluctuations. However, it can be uncomfortable for some, and can have an increased risk for an infection in the penetrated area. The invasive nature of continuous methods can also make it uncomfortable for some, reducing the likelihood of using one. [16]

Glucose sensors are some of the most known types of wearable sensors that use invasive methods for continuous monitoring. Glucose sensors use microneedles to measure interstitial fluid (ISF), as shown in figure 5. It is used instead of blood and plasma since it gives similar results. Such sensors are usually patches that are attached to the skin. Microneedles in the patches don't usually penetrate nerves or blood vessels at all, since ISF can be detected from the micro hole that the needles generate. This makes the process minimally invasive. ISF sample is then sent to the glucose sensor via microneedles and the data it provides is transmitted to a readout system. [17]

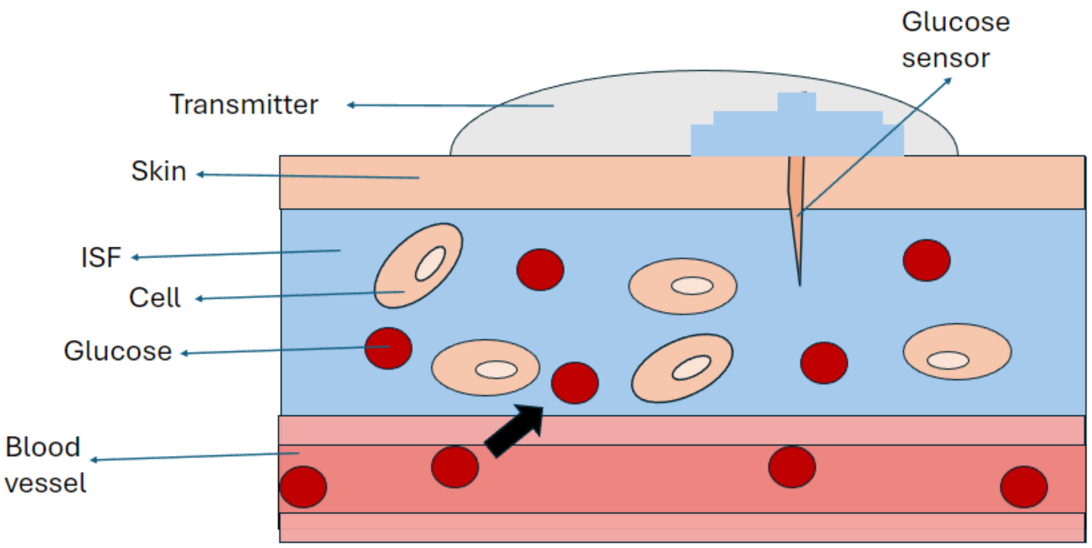

Figure 5. Basic principles of a wearable glucose sensor with minimally invasive sampling technique. Drawn using PowerPoint by Jerry Ylinen.

4.1.2 Non-invasive

Non-invasive methods gather information without puncturing the skin. The samples used usually are sweat and saliva, also urine, ISF and tears can be used. In hormone sensing, sweat and saliva are most potential ones. [18]

Non-invasive methods allow for ultimate convenience and the possibility of continuous measurement of hormone levels. [19] Improved comfortability allows continuous sensing for extended periods of time, leading to increase the usage of the device. However, current efforts of non-invasive methods lack accuracy. Hormone levels in external samples are small and the detection can be hard. Samples used can also be prone to external factors that can alter the results or make errors in detection. [20]

The number of non-invasive methods is growing and some of them have already been revealed to the public. Caltech researchers have developed a way of microfluidic sweat sampling with finger-worn sensor. This device uses short-stranded DNA, known as aptamers, to detect estradiol levels from sweat samples. Aptamers in this device resemble artificial antibodies where the estradiol is then attached and specifically detected. The plan for this device is to furthermore be miniaturized into a ring form to gain comfortability.

GlucoModicum's non-invasive technology utilises magnetohydrodynamics (MHD) to detect ISF without the need for needles. [21] This could allow for wearable sensors and remote measurements just the way glucose sensors nowadays do but without being invasive. [22]

5 Sensor Materials

Advancements in sensor technologies have been made with innovative materials to achieve accurate and accessible healthcare solutions. In the field of healthcare, a wide variety of materials can be used. However, for sensor compatible materials this section will focus on the following: graphene, carbon nanotubes, and biological molecules. These stand out from the rest for their unique properties and multiple applications in hormone monitoring development.

Materials chosen based on the properties they have. Especially in the sensor's material selections is crucial. Recognition layer needs to selectively detect the measured analyte, ignoring anything else present in the sample. This is acquired by selecting a material that has the right chemical properties to detect the wanted molecule of interest.

Biocompability is also a critical consideration in sensors, since it is in direct contact with the human body. Selecting materials for sensors ensuring biocompability is a priority.

Single materials usually don't offer all the properties needed. This is why in sensors detection layer, transductor and substrate are usually different materials. For example, detection layer needs to be sensitive and selective, transductor needs to be able to produce higher signal and substrate needs to be mechanically stable. Materials are chosen based on the properties needed and this results in the combination of multiple materials used in sensors. [23]

5.1 Graphene

Graphene is a single layer of carbon atoms arranged into a two-dimensional array made of hexagonal shapes, as shown in figure 6. It has a good conductivity it can cover a big surface and has good mechanical strength. Some of the graphene-based materials that have been studied to be used in sensors include graphene oxide (GO) and reduced graphene oxide (rGO). GO is oxidized from graphene and rGO is produced from GO by reducing the oxygen content.

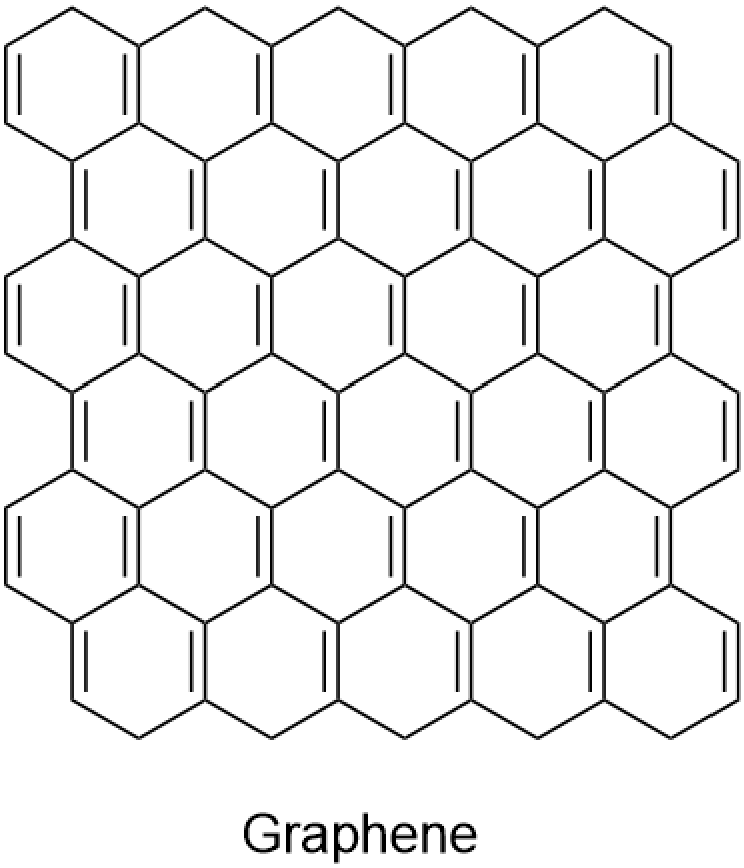

Figure 6. Graphene's two-dimensional array. Drawn using ChemDraw by Jerry Ylinen.

GO has insulating properties due to the oxygen present in it. It can form stable dispersions in polar solvents what makes it a good material for sensors. The dispersity mixed with the good biocompability makes it a useful material in biomedical applications. Its surface can be modified to fit better for certain applications. [24]

rGO has a higher conductivity than GO due to the partial sp^2 interactions. It has some structural interferences due to the reaction process. It can maintain a big surface area hence its use in energy storages and sensors. It is typically used in electronic devices as a conductive coating and is better suitable for that than GO due to the better conductivity. [24]

Both have been extensively studied for their help in selective hormone detection. Graphene based materials combined with metal nanoparticles have proven to be effective. Platinum and gold nanoparticles paired with graphene have been proven to enhance the conductivity. These hybrid materials have better conductivity than any single nanomaterial. Graphene's conductivity with the help of nanoparticles provides a quick detection of hormonal changes. It is especially useful especially in electrochemical sensors since it can detect the change very well. [25]

The big surface area that graphene-based materials provide allows for an extremely sensitive hormone sensor. The surface chemistry of graphene can be modified to improve selectivity to certain hormones. Graphene based materials have shown good biocompability which make them also good for in vivo sensing. This could involve implantable continuous sensing.

5.2 Carbon nanotubes

Carbon nanotubes are cylindrical nanostructures made of rolled up sheets of graphene. They are separated into two primary forms: single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT), as shown in figure 7. Carbon nanotubes have many of the properties of graphene but can be used in unique ways due to the shape of the structure.

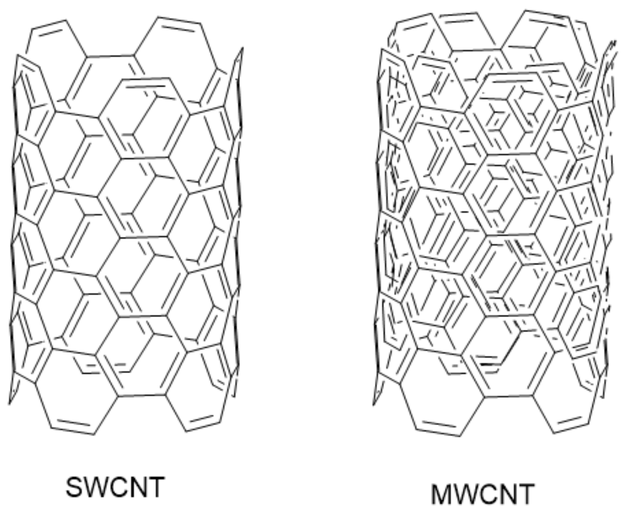

Figure 7. Two main forms of carbon nanotubes: SWCNT (left), MWCNT (right). Drawn using ChemDraw by Jerry Ylinen.

Carbon nanotubes can offer high surface to volume ratios which increases the sensitivity of hormone sensors. Sensitivity is acquired by the high number of interactions between the nanotubes and the measured molecule. Carbon nanotubes exhibit good electron transport properties. Rapid electron transfer enables fast response times in sensing applications.

Like rGO and GO, the surface of nanotubes can be modified with various chemicals or biomolecules to improve selectivity towards certain hormones. Modifying the surface with metal nanoparticles can also improve the conductivity a lot. Incorporation of metal nanoparticles on the surface of carbon nanotubes enhances the conductivity, leading to improved sensor performance and accuracy. [26]

5.3 Biological molecules

Biological molecules play a big role in sensor technologies and have been proven to be useful particularly in detecting biological analytes such as hormones. Among these molecules, antibodies and aptamers are widely used in the recognition process. Antibodies are used in immunoassays as the detection of analyte while aptamers can have the same function in certain sensor technologies.

Aptamers are used less but show a great potential in the field of hormone sensing. Aptamers are a short strand of DNA that have a high binding affinity towards specific molecules, including proteins, cells, and other small molecules. They are synthesized with a ligand enrichment process.

Aptamers are superior compared to traditional processes. They are cheap and can be made in large quantities. They are also superior in terms of specificity and can be generated for certain molecules. This is a highly valuable asset in sensor materials as it addresses the issue of many possible interferences in the body. Aptamers are also used in the micro fluidical sweat analysis previously mentioned in the Caltech research. [27]

6 Summary

The rapid advancements in health research and technology show the need to further explore female physiology and hormones. Current female hormone monitoring methods, lab tests and home kits, are limited in accessibility and user-friendliness. For that reason, there is a demand for innovative technologies, especially for those that could enhance accuracy and convenience. Female hormone monitoring has a considerable importance in multiple aspects, fertility, hormonal balance, drug dosing, and overall health monitoring.

Gender inequality persist in health research and women are often underrepresented in clinical studies. This exclusion can lead to delayed diagnoses, misdiagnoses, and adverse drug responses. Especially differences in hormone levels and physiological responses between genders affect the results. For that reason, there is a need for gender specific research to overcome and improve issues in female hormone monitoring.

The conventional methods of measuring hormones, such as immunoassays, ELISA, RIA, FIA, and chromatography have advantages and limitations. However emerging sensor technologies offer promising alternatives, including wearable patches and saliva-based continuous monitoring that are minimally to non-invasive. These sensors detect physical, chemical, or biological changes that can be detected.

Materials like graphene and carbon nanotubes show huge potential in hormone sensor development. They have a high conductivity, large surface area that increases sensitivity and biocompability. These materials combined with metal nanoparticles or biological molecules, enhance the sensor’s sensitivity and selectivity.

In conclusion, adopting innovative technologies and materials to help with current problems a lot can be improved. They can help with the advancing healthcare systems and improve outcomes for individuals, across all stages of life.

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