

6.0 EPILOGUE

6.1	SUMMARY	141
6.2	CONCLUSION	145
6.3	CONCLUDING REMARKS	146

6.0 EPILOGUE

6.1 SUMMARY

Cancer is the leading fatal disease which haunts^s the human imagination. There is no apparent increase in overall cure rate. The bottom line is that cancer is becoming^{more} common~~er~~, poorly understood and impossible to avoid. In spite of dedicated efforts of the people working in the field, no major breakthrough has come out or is anticipated in this area. The single most important factor that is known to improve the end results of cancer are early diagnosis, improved prognostication and better management. Circulating tumour markers can be helpful in these aspects because blood is the major route for spread of disease. The participation of better tumour markers in diagnosis and management of cancer can significantly benefit the patients as well as clinicians. Breast and oral cavity are most common sites for cancer incidence among females and males, respectively with the increasing incidence rate, year after year, in people of Gujarat, India. The diagnosis and management of these malignancies have an important impact on the social well being of patients. These points have provided us a rationale to select breast cancer and oral cavity cancer for present series of investigations. Healthy individuals were included in the study to define normal range of the markers. The patients with benign/precancerous conditions were included to evaluate specificity of the markers. Our understanding of the role of glycoproteins in cancer is growing rapidly and some preventive measures are now obvious but much remains to be learned. As stated at the onset, the present investigation was undertaken to evaluate comprehensive glycoprotein changes in cancer patients.

The choice of glycoproteins, glycoprotein constituents and enzymes associated with glycoprotein metabolism was guided by several considerations such as: (i) association of altered glycosylation with malignancy, (ii) the role attributed to

them in cell surface functions and alterations of cell surface are obvious during malignant transformation and (iii) majorities of today's most widely used tumour markers are glycoprotein in nature.

The study included different forms of sialic acid (viz. free, protein bound and total), fucose, and seromucoid fraction because of the fact that these are important constituents of glycoproteins. The levels of these constituents were normalized by total protein to check the alterations in glycosylation during malignancy. Other parameter selected was glycoprotein electrophoretic patterns. The investigations were also made to study alterations in the enzymes including fucosidase, fucosyl transferase, and sialyl transferase. The separation of sialoproteins and fucoproteins was also carried out. ***The data emerged from the study can be summarized as under:***

1. In both group of cancer patients, the concentrations of sialic acid forms, fucose, mucoid proteins and hexoses as well as their ratio to total proteins were significantly higher in untreated cancer patient as compared to the controls.
2. The levels of glycoprotein constituents were increased in patients with BBD/OPC as compared to the controls.
3. The value of total sialic acid, ratio of total sialic acid to total protein, ratio of fucose to total protein and ratio of mucoid proteins to total proteins exhibited statistically significant elevations in patients with BBD as compared to healthy females.
4. The concentrations of free and total sialic acid, total sialic acid to total protein ratio, mucoid proteins, hexoses and mucoid proteins to total protein ratio were significantly higher in patients with OPC as compared to the controls.
5. Among breast cancer patients, except protein bound sialic acid to total protein ratio, all other constituents were significantly higher as compared to patients with BBD.

6. Glycoprotein constituents were significantly increased in untreated oral cavity cancer patients as compared to the patients with OPC.
7. Levels of the markers correlated well with the extent of malignant disease. All the glycoprotein constituents showed positive correlation. However, correlation was statistically significant in case of total sialic acid, fucose, fucose to total protein ratio, hexoses and hexoses to total protein ratio in both the groups of cancer patients. Further, in case of breast cancer patients, free and protein bound sialic acid, protein bound sialic acid to total protein ratio and mucoid proteins to total protein ratio also showed significant correlation with the stage of the disease.
8. Higher levels of ratio of total sialic acid to total proteins, ratio of protein bound sialic acid to total proteins, fucose and its ratio to total proteins, mucoid proteins and its ratio to total proteins were associated with poor survival in both the groups of cancer patients. Among breast cancer patients, levels of total sialic acid, hexoses and its ratio to total proteins were also associated with poor survival.
9. ROC curves revealed that the glycoprotein constituents have ability to discriminate cancer patients from healthy population.
10. Values of the glycoprotein constituents were declined near to normal levels in patients with favourable treatment outcome. Except free sialic acid, all other parameters were significantly higher in nonresponders as compared to the responders.
11. Mean values of albumin region glycoproteins were lower in cancer patients as compared to the patients with BBD/OPC. The gamma fraction glycoproteins were higher in untreated cancer patients as compared to the controls and pathological controls. Mean values of albumin and gamma region glycoproteins did not show significant variations. However, ratio of albumin region glycoproteins to total protein was significantly declined in untreated cancer patients and ratio of gamma region glycoproteins to total proteins showed significant elevations in cancer patients as compared to the controls.

Further, the ratio of albumin to gamma region glycoproteins showed significant decline in untreated cancer patients as compared to the controls.

12. An extra glycoprotein band was found between beta and gamma region. The frequency of this band was higher in untreated cancer patients as compared to the controls and pathological controls. Further, the frequency of this band was higher in cancer patients as compared to the controls. During comparison between pretreatment and follow-up levels, albumin, alpha and beta region glycoproteins showed elevations in responders as compared to both nonresponders and untreated cancer patients. However, gamma region glycoproteins showed the reverse trend. The ratio of albumin to gamma region glycoproteins showed elevations in responders.
13. Among the enzymes studied, sialyl transferase and fucosyl transferase showed significant elevations in untreated oral cavity cancer and breast cancer patients as compared to their respective controls. Levels of these enzymes were higher in patients with BBD/OPC as compared to the controls. The levels of sialyl transferase and fucosyl transferase were significantly higher in untreated cancer and oral cavity cancer patients as compared to the patients with BBD and OPC, respectively. The activity of fucosidase was significantly lower in untreated cancer patients as compared to the controls. Fucosidase levels were higher in patients with BBD/OPC as compared to patients with breast cancer and oral cavity cancer. Levels of the enzyme were found to be lower in patients with BBD/OPC as compared to their respective controls. Fucosidase levels were significantly higher in responders as compared to untreated cancer patients as well as nonresponders.
14. Lectin affinity study revealed higher amount of sialoproteins and fucoproteins in untreated cancer patients as compared to both, controls as well as pathological controls. The degree of sialylation and fucosylation was higher in patients with BBD/OPC as compared to the respective controls. The nonresponders showed similar patterns of sialoproteins and fucoproteins when compared with untreated cancer patients.

15. The changes in sialoproteins and fucoproteins correlated well with the alterations in levels of sialic acid and fucose as well as with the activities of sialyl transferase and fucosyl transferase.
16. Tumor tissues showed elevations in the levels of glycoprotein constituents, sialyl transferase and fucosyl transferase as compared to normal surrounding tissues. The alterations in glycoprotein constituents and enzymes in circulation were in accordance with the changes in malignant tumors.

6.2 CONCLUSION

This multi-parametric study provided vital informations about the diagnosis, prognostication and treatment outcome of patients with breast and oral cavity cancer. The glycoprotein constituents were independently associated with stage of the disease and poor prognosis of the patients. Furthermore, the data suggested that continuously raised levels of glycoprotein constituents were associated with poor treatment outcome. This may indicate presence of occult malignant disease and/or persistent malignant disease. The patients with increased levels of glycoprotein constituents should also be considered as a high risk group for the development of recurrence/metastasis. This can warn the clinicians for better treatment modalities. These being a simple technique may be used as an adjunct in the diagnosis, prognostication and treatment monitoring of cancer patients. The alterations in glycoprotein constituents also correlated with the alterations in enzyme levels and glycoprotein electrophoretic patterns. The study suggest that the alterations in glycoprotein constituents are due to the alterations in glycoprotein metabolism. The changes in sialoproteins and fucoproteins in sequential follow-up blood samples can be useful to establish the exact alterations in the carbohydrate moieties during malignancy. The glycoprotein changes have a distinct clinical relevance for patients with breast cancer and oral cavity cancer. The analysis of glycoprotein constituents, fucosidase and glycoprotein electrophoresis is easy to perform on routine basis. This can be helpful in diagnosis, prognostication and treatment monitoring and

thus, can provide more effectively tailored treatment regimes in addition to routine process.

6.3 CONCLUDING REMARKS

In recent years, the clinicians, pathologists and researchers have found themselves facing numerous additional challenges and opportunities. The present study tried to figure out careful evaluation of glycoprotein changes which can form strategies and tactics for cancer diagnosis and management at the stages of cancer occurrence and disease progression. ***In furtherance***, specific proteins which are associated with presence of malignancy need to be isolated purified and characterized. The isoenzymes of sialyl transferase and fucosyl transferase should be studied using iso-electro^{ic} focusing technique. Quantitaion of mucins in circulation by detection of circulatory immune complexes in breast cancer and oral cavity cancer as well as evaluation[^] the glycoprotein changes in saliva of patients with OPC and oral cavity cancer can add more significant data in the subject of ***glycoproteins and cancer***.